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Ambient Water Quality Criteria: Dichlorobenzenes

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzene. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a , ...

KEYWORDS: *Water quality, *Toxicology, *Chlorobenzenes, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Benzene/dichloro, *Water pollution effects(Plants).

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PB 292429

DICHLOROBENZENES

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

DICHLOROBENZENES

CRITERIA

Aquatic Life

1,2-dichlorobenzene

For 1,2-dichlorobenzene the criterion to protect freshwater aquatic life as derived using the Guidelines is 44 µg/l as a 24-hour average and the concentration should never exceed 99 µg/l at any time.

For 1,2-dichlorobenzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 15 µg/l as a 24-hour average concentration should not exceed 34 µg/l at any time.

1,3-dichlorobenzene

For 1,3-dichlorobenzene the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 310 µg/l as a 24-hour average and the concentration should not exceed 700 µg/l at any time.

For 1,3-dichlorobenzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 22 µg/l as a 24-hour average and the concentration should not exceed 49 µg/l at any time.

1,4-dichlorobenzene

For 1,4-dichlorobenzene the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 190 µg/l as a 24-hour average and the concentration should not exceed 440 µg/l at any time.

For 1,4-dichlorobenzene the criterion to protect salt-water aquatic life as derived using procedures other than the Guidelines is 15 µg/l as a 24-hour average and the concentrations should not exceed 34 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of dichlorobenzene ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 230 µg/l total dichlorobenzene (all isomers combined).

Introduction

The dichlorobenzenes are a class of halogenated aromatic compounds represented by three structurally similar isomers: 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzene (Weast, 1975). Dichlorobenzenes have the molecular formula $C_6H_4Cl_2$ and a molecular weight of 147.01 (Weast, 1975).

1,2-Dichloro- (1,2-DCB) and 1,3-dichlorobenzene (1,3-DCB) are liquids at normal environmental temperatures while 1,4-dichlorobenzene (1,4-DCB) is a solid (Weast, 1975). Melting points (MP), boiling points (BP) and densities for the three isomers are presented in Table 1 (Weast, 1975).

TABLE 1 - (Weast, 1975)

Compound	MP (deg.C)	BP (deg.C)	Density (deg.C)
1,2-dichlorobenzene	-17.6	179	1.30 g/ml (20)
1,3-dichlorobenzene	-24.2	172	1.29 g/ml (20)
1,4-dichlorobenzene	53.0	174	1.25 g/ml (20)

The dichlorobenzenes are soluble in water at concentrations which are toxic to aquatic organisms. The solubilities in water of the 1,2-, 1,3,-, and 1,4,-dichlorobenzene isomers at 25 degrees C are 145,000 µg/l, 123,000 µg/l, and 80,000 µg/l, respectively (Jacobs, 1957). The dichlorobenzenes also are readily soluble in natural fats or fat soluble substances (Windholz, 1976). The logs of the octanol/water partition coefficients for 1,3-dichloro-, and 1,4-dichlorobenzene are 3.44 and 3.37, respectively (U.S. EPA, 1978). All three dichlorobenzene isomers are relatively volatile.

The vapor pressure of 1,2-dichlorobenzene at 20 degrees C is 1 mm Hg; the vapor pressure of 1,3-dichlorobenzene at 39 degrees C is 5 mm Hg; and the vapor pressure of 1,4-dichlorobenzene at 25 degrees C is 0.4 mm Hg (Jordan, 1954; Kirk and Othmer, 1963).

The major uses of 1,2-DCB are as a process solvent in the manufacturing of toluene diisocyanate and as a intermediate in the synthesis of dyestuffs, herbicides, and degreasers (West and Ware, 1977). 1,4-Dichlorobenzene is used primarily as an air deodorant and an insecticide, which account for 90 percent of the total production of this isomer (West and Ware, 1977). Information is not available concerning the production and use of 1,3-DCB. However, it may occur as a contaminant of 1,2- or 1,4-DCB formulations. Both 1,2-dichloro- and 1,4-dichlorobenzene are produced almost entirely as byproducts during the production of monochlorobenzene. Combined annual production of these two isomers is the United States approaches 50,000 metric tons (West and Ware, 1977).

Dichlorobenzenes have been detected at various conentrations in ambient water, groundwater, and finished drinking water. They have been found to bioconcentrate in fish tissues.

Human exposure to dichlorobenzene is reported to cause hemolytic anemia and liver necrosis, and 1,4-dichlorobenzene has been found in human adipose tissue. In addition, the dichlorobenzenes are toxic to non-human mammals, birds, and aquatic organisms and impart an offensive taste and odor to water. The dichlorobenzenes are metabolized by mammals, including humans, to various dichlorophenols, some of which are as toxic as the dichlorobenzenes.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Comparable data for the bluegill, Daphnia magna, and Selenastrum capricornutum (an alga) suggest no appreciable differences in the toxicity of 1,2-, 1,3-, and 1,4-dichlorobenzene. All these tests were conducted under static conditions and the test concentrations were not measured. These data also suggest that there is little difference between the bluegill and Daphnia magna when unadjusted values are compared. The alga, based on chlorophyll a and cell numbers, has higher 96-hour EC50 values.

Acute Toxicity

The bluegill has been tested under similar conditions (U.S. EPA, 1978) and the 96-hour LC50 values, adjusted according to the Guidelines for static and unmeasured test conditions, are 3,060, 2,740, and 2,340 g/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively (Table 1). These results indicate that the position of the chlorine atoms on the benzene ring probably does not influence the toxicity of dichlorobenzenes very much. Dawson, et al. (1977) also tested the bluegill and their adjusted 96-hour LC50 was 15,000 µg/l for 1,2-dichlorobenzene; this is different from

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506- (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

that (3,060 µg/l) for the same species by different investigators (U.S. EPA, 1978). This difference may be due to the fact that Dawson, et al. (1977) added 1,2-dichlorobenzene to the surface of the test water without the subsequent mixing usually done for such tests. The Final Fish Acute Value, derived by dividing the geometric mean values for each dichlorobenzene by the Guidelines sensitivity factor of 3.9, are 1,700, 700, and 600 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively.

When the unadjusted 96-hour LC50 values obtained for the bluegill under similar conditions (U.S. EPA, 1978), for the dichlorobenzenes and a variety of other chlorinated benzenes (chlorobenzene, trichlorobenzene, tetrachlorobenzene and pentachlorobenzene) are compared, there is good correlation between the degree of chlorination and acute toxicity. (See the criterion document for chlorinated benzenes for details.) These LC50 values range from 15,900 ug/l for chlorobenzene to 250 µg/l for pentachlorobenzene with the dichlorobenzenes approximately three times more toxic than chlorobenzene. Correlations between toxicity and structural characteristics can be useful in the derivation of criteria.

Daphnia magna is the only freshwater invertebrate species for which data for dichlorobenzenes were available (Table 2). These data were obtained using similar methods (U.S. EPA, 1978) and the adjusted 48-hour EC50 values are 2,070, 23,800, and 9,320 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. As stated earlier, there is no great difference

in sensitivity between the bluegill and Daphnia magna when unadjusted LC50 values are compared. However, since the sensitivity factor (21) for the invertebrate species is larger than that (3.9) for fish, the resultant Final Acute Values are based on the Final Invertebrate Acute Values of 99 and 440 µg/l for 1,2-, and 1,4-dichlorobenzene, respectively. However, the Final Fish Acute Value (700 µg/l) for 1,3-dichlorobenzene becomes the Final Acute Value for that chemical since the Final Invertebrate Acute Value (1,100 µg/l) is higher.

As with the bluegill, comparable test results (U.S. EPA, 1978) with other chlorinated benzenes and Daphnia magna are available. The unadjusted 48-hour EC50 values range from 86,000 µg/l for chlorobenzene to 5,280 µg/l for pentachlorobenzene, again indicating an increase in toxicity of the chlorinated benzenes with increasing chlorination.

Chronic Toxicity

An embryo-larval test with fathead minnows and 1,2-dichlorobenzene has been conducted (U.S. EPA, 1978) and the chronic value for this test is 1,000 µg/l (Table 3). No other data on chronic effects on fish or invertebrate species are available. The final Fish Chronic Value for 1,2-dichlorobenzene is the chronic value of 1,000 µg/l divided by the sensitivity factor (6.7) or 150 µg/l.

Plant Effects

The alga, Selenastrum capricornutum, has been tested for the effects of dichlorobenzenes on chlorophyll a and cell numbers (Table 4). The EC50 values range from 91,600

to 179,000 µg/l for the dichlorobenzenes, indicating little if any relationship to the location of chlorine atoms on the benzene ring. The Final Plant Values are 91,600, 149,000, and 96,700 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorinated benzenes and, as with the bluegill and Daphnia magna, toxicity is increased with an increase in chlorination. The lowest plant values range from 224,000 µg/l for chlorobenzene to 6,630 µg/l for pentachlorobenzene.

Residues

Bioconcentration by the bluegill (Table 5) has been studied using ^{14}C-labeled dichlorobenzenes, with thin layer chromatography for verification (U.S. EPA, 1978). The bioconcentration factors were 89, 66, and 60 for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. Equilibrium occurred in less than 14 days and the half-life for each dichlorobenzene was less than 1 day. These results suggest that the dichlorobenzenes are unlikely to be a tissue residue problem in the aquatic environment.

Additional comparable data (U.S. EPA, 1978) are available in the chlorinated benzenes criterion document for tetrachlorobenzene and pentachlorobenzene and the bluegill. These compounds are much more lipophilic than the dichlorobenzenes with bioconcentration factors of 1,800 for tetrachlorobenzene and 3,400 for pentachlorobenzene. Hexachlorobenzene has been tested with the pinfish and the bioconcentration factor was 23,000. In addition, the half-lives of chlorinated

benzenes increase with chlorination from less than 1 day for the dichlorobenzenes to 2 to 4 days for tetrachlorobenzene and greater than 7 days for pentachlorobenzene. These results indicate that the environmental risk due to tissue residues increases with increasing chlorination and support the conclusion above that dichlorobenzenes will not likely cause an undue residue problem for aquatic life.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

1,2-dichlorobenzene

Final Fish Acute Value = 1,700 µg/l

Final Invertebrate Acute Value = 99 µg/l

Final Acute Value = 99 µg/l

Final Fish Chronic Value = 150 µg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = 92,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 150 µg/l

0.44 x Final Acute Value = 44 µg/l

1,3-dichlorobenzene

Final Fish Acute Value = 700 µg/l

Final Invertebrate Acute Value = 1,100 µg/l

Final Acute Value = 700 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 150,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 150,000 µg/l

0.44 x Final Acute Value = 310 µg/l

1,4-dichlorobenzene

Final Fish Acute Value = 600 µg/l

Final Invertebrate Acute Value = 440 µg/l

Final Acute Value = 440 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 97,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 97,000 µg/l

0.44 x Final Acute Value = 190 µg/l

The maximum concentration of 1,2-dichlorobenzene is the Final Acute Value of 99 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effect on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,2-dichlorobenzene the criterion to protect freshwater aquatic life as derived using the Guidelines is 44 µg/l as a 24-hour average and the concentration should never exceed 99 µg/l at any time.

No freshwater criterion can be derived for either 1,3-dichlorobenzene of 1,4-dichlorobenzene using the Guidelines because no Final Chronic Value for either fish or invertebrate

species or a good substitute for either value is available for either compound.

However, results obtained with 1,2-dichlorobenzene and freshwater organisms indicate how criteria for other dichlorobenzenes may be estimated.

The Final Chronic Value for 1,2-dichlorobenzene and freshwater organisms is greater than 0.44 times the Final Acute Value, even though a chronic value is available for fish. Therefore, it seems reasonable to estimate criteria for other dichlorobenzenes and freshwater organisms using 0.44 times the Final Acute Value.

To estimate a criterion for 1,3-dichlorobenzene, the maximum concentration is the Final Acute Value of 700 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,3-dichlorobenzene the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 310 µg/l as a 24-hour average and the concentration should never exceed 700 µg/l at any time.

To estimate a criterion for 1,4-dichlorobenzene, the maximum concentration is the Final Acute Value of 440 µg/l and the 24-hour average concentration is 0.44 times the

Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,4-dichlorobenzene the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 190 µg/l as a 24-hour average and the concentration should never exceed 440 µg/l at any time.

Table 1. Freshwater fish acute values for dichlorobenzenes

Organism	Biomassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill, Lepomis macrochirus	S	U	1,2-dichloro-benzene	96	27,000	15,000	Dawson, et al. 1977
Bluegill, Lepomis macrochirus	S	U	1,2-dichloro-benzene	96	5,590	3,060	U.S. EPA, 1978
Bluegill, Lepomis macrochirus	S	U	1,3-dichloro-benzene	96	5,020	2,740	U.S. EPA, 1978
Bluegill, Lepomis macrochirus	S	U	1,4-dichloro-benzene	96	4,280	2,340	U.S. EPA, 1978

* S = static

** U = unmeasured

Geometric mean of adjusted values: 1,2-dichlorobenzene = 6,770 µg/l $\frac{6,770}{3.9}$ = 1,700 µg/l

1,3-dichlorobenzene = 2,740 µg/l $\frac{2,740}{3.9}$ = 700 µg/l

1,4-dichlorobenzene = 2,340 µg/l $\frac{2,340}{3.9}$ = 600 µg/l

Table 2. Freshwater invertebrate acute values for dichlorobenzenes (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, Daphnia magna	S	U	1,2-dichloro-benzene	48	2,440	2,070
Cladoceran, Daphnia magna	S	U	1,3-dichloro-benzene	48	28,100	23,800
Cladoceran, Daphnia magna	S	U	1,4-dichloro-benzene	48	11,000	9,320

* S = static

** U = unmeasured

Geometric mean of adjusted values:

1,2-dichlorobenzene = 2,070 µg/l $\quad \frac{2,070}{21} = 99$ µg/l

1,3-dichlorobenzene = 23,800 µg/l $\quad \frac{23,800}{21} = 1,100$ µg/l

1,4-dichlorobenzene = 9,320 µg/l $\quad \frac{9,320}{21} = 440$ µg/l

Table 3. Freshwater fish chronic values for dichlorobenzenes (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
		1,2-dichlorobenzene	
Fathead minnow, *Pimephales promelas*	E-L	1,600-2,500	1,000

* E-L = embryo-larval

Geometric mean of chronic values = 1,000 µg/l $\quad \frac{1,000}{6.7}$ = 150 µg/l

Lowest chronic value = 1,000 µg/l

Table 4. Freshwater plant effects for dichlorobenzenes (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
	1,2-dichlorobenzene	
Alga, Selenastrum capricornutum	EC50 96-hr chlorophyll a	91,600
Alga, Selenastrum capricornutum	EC50 96-hr cell number	98,000
	1,3-dichlorobenzene	
Alga, Selenastrum capricornutum	EC50 96-hr chlorophyll a	179,000
Alga, Selenastrum capricornutum	EC50 96-hr cell number	149,000
	1,4-dichlorobenzene	
Alga, Selenastrum capricornutum	EC50 96-hr chlorophyll a	98,100
Alga, Selenastrum capricornutum	EC50 96-hr cell number	96,700

Lowest plant value: 1,2-dichlorobenzene = 91,600 µg/l

1,3-dichlorobenzene = 149,000 µg/l

1,4-dichlorobenzene = 96,700 µg/l

Table 5. Freshwater residues for dichlorobenzenes (U.S. EPA, 1978)

Organism	Bioconcentration Factor	Time (days)
	1,2-dichlorobenzene	
Bluegill, *Lepomis macrochirus*	89	14
	1,3-dichlorobenzene	
Bluegill, *Lepomis macrochirus*	66	14
	1,4-dichlorobenzene	
Bluegill, *Lepomis macrochirus*	60	14

SALTWATER ORGANISMS

Introduction

The data base for toxicity of the dichlorobenzenes is limited to results of acute exposures of fish, invertebrate, and phytoplankton species, predominantly performed with unmeasured concentrations under static test conditions. The LC50 and plant values range from 1,970 to greater than 100,000 µg/l; the mysid shrimp was most sensitive. Although differences in acute toxicity of the dichlorobenzenes exist between species, the toxicity of dichlorobenzenes to individual species is similar so for practical purposes they may be considered to be equally toxic.

Acute Toxicity

The sheepshead minnow was similarly sensitive to the dichlorobenzenes; unadjusted 96-hour LC50's ranged from 9,660 to 7,400 µg/l (Table 6). Toxicity of these compounds to fishes may be inadequatley estimated by these results since data on only one other fish species are available. The tidewater silversides (Dawson, et al. 1977) was as sensitive as the sheepshead minnow with an unadjusted 96-hour LC50 of 7,300 µg/l. The Final Fish Acute Values derived from these data are 1,200, 1,100, and 1,100 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively.

Comparable data (U.S. EPA, 1978) are available for the sheepshead minnow and other chlorinated benzenes. (See the criterion document for chlorinated benzenes for details.) These LC50 values range from 10,500 µg/l for chlorobenzene

to 830 µg/l for pentachlorobenzene and indicate a good correlation between the degree of chlorination and acute toxicity.

The mysid shrimp was more sensitive to the dichlorobenzenes in 96-hour acute exposures (Table 7) than were the fish; LC50's ranged from 1,970 to 2,850 µg/l. The Final Invertebrate Acute Values and thus the Fianl Acute Values for these compounds are 34, 49, and 34 µg/l for 1,2-, 2,3-, and 1,4-dichlorobenzene, respectively.

As with the sheepshead minnow, comparable test results (U.S. EPA, 1978) with other chlorinated benzenes and the mysid shrimp are available. The unadjusted LC50 values range from 16,400 µg/l for chlorobenzene to 160 µg/l for pentachlorobenzene, again indicating an increase in toxicity of the chlorinated benzenes with increasing chlorination. Correlations of toxicity and chemical structure such as this can be useful in deriving criteria.

Chronic Toxicity

The chronic effects of the dichlorobenzenes on saltwater fish and invertebrate species have not been studied.

Plant Effects

One algal species, Skeletonema costatum, has been tested (U.S. EPA, 1978) for acute effects of exposure to the dichlorobenzenes (Table 8). The EC50 values for cell number of chlorophyll a ranged from 44,100 to 59,100 µg/l. The Final Plant Values are 44,100, 49,600, and 54,800 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorinated benzenes and, as with the sheepshead

minnow and mysid shrimp, toxicity generally increased with an increase in chlorination. The lowest plant values ranged from 341,000 µg/l for chlorobenzene to 1,980 µg/l for pentachlorobenzene.

Miscellaneous

Two polychaete worm species and clam embryos and larvae were relatively insensitive to exposures to 1,2-, and 1,4-dichlorobenzene (Table 9). The LC50 values for 1,2-dichlorobenzene and clam embryos and larvae were greater than 100,000 µg/l (Davis and Hindu, 1969). Acute exposures to 1,2-, and 1,4-dichlorobenzene at 100,000 µg/l were responsible for 55-100 percent emergence of two polychaete species from parasitized oysters (Mackenzie and Shearer, 1959).

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

1,2-dichlorobenzene

Final Fish Acute Value = 1,200 µg/l

Final Invertebrate Acute Value = 34 µg/l

Final Acute Value = 34 µg/l

Final Fish Chronic Value = not available

Final Plant Value = 44,000 µg/l

Residue Limited Toxicant Concentration = not availble

Final Chronic Value = 44,000 µg/l

0.44 x Final Acute Value = 15 µg/l

1,3-dichlorobenzene

Final Fish Acute Value = 1,100 µg/l

Final Invertebrate Acute Value = 49µg/l

Final Acute Value = 49 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 50,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 50,000 µg/l

0.44 x Final Acute Value = 22 µg/l

1,4-dichlorobenzene

Final Fish Acute Value = 1,100 µg/l

Final Invertebrate Acute Value = 34 µg/l

Final Acute Value = 34 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 55,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Vale = 55,000 µg/l

0.44 x Final Acute Value = 15 µg/l

No saltwater criterion can be derived for any dichlorobenzene using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, results obtained with 1,2-dichlorobenzene and freshwater organisms indicate how criteria may be estimated for the dichlorobenzenes.

The Final Chronic Value for 1,2-dichlorobenzene and freshwater organisms is greater than 0.44 times the Final Acute Value, even though a chronic value is available for fish. Therefore, it seems reasonable to estimate criteria for dichlorobenzenes and saltwater organisms using 0.44 times the Final Acute Value.

To estimate a criterion for 1,2-dichlorobenzene, the maximum concentration is the Final Acute Value of 34 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,2-dichlorobenzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 15 ug/l as a 24-hour average and the concentration should never exceed 34 ug/l at any time.

To estimate a criterion for 1,3-dichlorobenzene, the maximum concentration is the Final Acute Value of 49 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,3-dichlorobenzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 22 µg/l as a 24-hour average and the concentration should never exceed 49 µg/l at any time.

To estimate a criterion for 1,4-dichlorobenzene, the maximum concentration is the Final Acute Value of 34 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwate aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,4-dichlorobenzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 15 µg/l as a 24-hour average and the concentration should never exceed 34 µg/l at any time.

Table 6. Marine fish acute values for dichlorobenzenes

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Tidewater silverside, Menidia beryllina	S	U	1,2-dichloro-benzene	96	7,300	3,991	Dawson, et al. 1977
Sheepshead minnow, Cyprinodon variegatus	S	U	1,2-dichloro-benzene	96	9,660	5,281	U.S. EPA, 1978
Sheepshead minnow, Cyprinodon variegatus	S	U	1,3-dichloro-benzene	96	7,770	4,248	U.S. EPA, 1978
Sheepshead minnow, Cyprinodon variegatus	S	U	1,4-dichloro-benzene	96	7,400	4,046	U.S. EPA, 1978

* S = static

** U = unmeasured

Geometric mean of adjusted values: 1,2-dichlorobenzene = 4,591 µg/l $\frac{4,591}{3.7}$ = 1,200 µg/l

1,3-dichlorobenzene = 4,248 µg/l $\frac{4,248}{3.7}$ = 1,100 µg/l

1,4-dichlorobenzene = 4,046 µg/l $\frac{4,046}{3.7}$ = 1,100 µg/l

Table 7. Marine invertebrate acute values for dichlorobenzenes (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, Mysidopsis bahia	S	U	1,2-dichloro-benzene	96	1,970	1,669
Mysid shrimp, Mysidopsis bahia	S	U	1,3-dichloro-benzene	96	2,850	2,414
Mysid shrimp, Mysidopsis bahia	S	U	1,4-dichloro-benzene	96	1,990	1,686

* S = static

** U = unmeasured

Geometric mean of adjusted values: 1,2-dichlorobenzene = 1,669 µg/l $\frac{1,669}{49}$ = 34 µg/l

1,3-dichlorobenzene = 2,414 µg/l $\frac{2,414}{49}$ = 49 µg/l

1,4-dichlorobenzene = 1,686 µg/l $\frac{1,686}{49}$ = 34 µg/l

Table 8. Marine plant effects for dichlorobenzenes (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
		1,2-dichlorobenzene
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	44,200
Alga, *Skeletonema costatum*	EC50 96-hr cell number	44,100
		1,3-dichlorobenzene
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	52,800
Alga, *Skeletonema costatum*	EC50 96-hr cell number	49,600
		1,4-dichlorobenzene
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	54,800
Alga, *Skeletonema costatum*	EC50 96-hr cell number	59,100

Final plant value: 1,2-dichlorobenzene = 44,100 µg/l

1,3-dichlorobenzene = 49,600 µg/l

1,4-dichlorobenzene = 54,800 µg/l

Table 9. Other marine data for dichlorobenzenes

Organism	Test Duration	Effect	Result (ug/l)	Reference
Polychaete worm, *Polydora websteri*	3 hrs	65% emergence from parasitized oysters	100,000 (1,2-dichlorobenzene)	Mackenzie & Shearer, 1959
Polychaete worm, *Nerlis* sp.	3 hrs	70% emergence from parasitized oysters	100,000 (1,2-dichlorobenzene)	Mackenzie & Shearer, 1959
Clam (embryo), *Mercenaria mercenaria*	48 hrs	LC50	>100,000 (1,2-dichlorobenzene)	Davis & Hindu, 1969
Clam (larva), *Mercenaria mercenaria*	12 days	LC50	>100,000 (1,2-dichlorobenzene)	Davis & Hindu, 1969
Polychaete worm, *Polydora websteri*	3 hrs	55% emergence from parasitized oysters	100,000 (1,4-dichlorobenzene)	Mackenzie & Shearer, 1959
Polychaete worm, *Nereis* sp.	3 hrs	100% emergence from parasitized oysters	100,000 (1,4-dichlorobenzene)	Mackenzie & Shearer, 1959

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EXPOSURE

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The production, use, transport, and disposal of dichlorobenzenes result in widespread dispersal to, and therefore contamination of, environmental media, with resulting opportunity for exposure of the biosphere (including man). Dichlorobenzenes have been detected or quantified in rivers, ground water, municipal and industrial discharges, drinking water, air, and soil. They have also been detected in tissues of lower organisms living in contaminated waters and in exposed higher animals. Persistence in the environment varies among compounds and with conditions, the more highly halogenated benzenes being more generally resistant to biodegradation, and persistent.

Table 2 shows detection and concentrations of DCB's in raw and contaminated waters. 1,2-DCB has been reported as entering water systems at average levels of 2 mg/l as a result of its use by industrial wastewater treatment plants for odor control (Ware and West, 1977, citing Kopp, 1977). 1,4-DCB enters wastewater systems because of its use in toilet blocks (Ware and West, 1977). Table 3 summarizes the data on DCB's in drinking water samples. Reported DCB levels in drinking water samples have thus far been relatively low (i.e., compared to trihalomethanes).

As with halomethanes, new chlorinated organic compounds including chlorinated benzenes have been reported to result from chlorination of raw and waste waters containing organic precursor material. Glaze, et al. (1976) reported the formation of many new chlorinated organic compounds as a result

Table 2. - Dichlorobenzenes in raw and discharge waters† (Ware & West, 1977)

Medium or Sample	Location	1,2-DCB	1,3-DCB	1,4-DCB	DCB
Ground water	Miami, Fla.	1(cce) d(voa)	0.5(cce) d(voa)	0.5(cce) d(voa)	
Raw water contam. with municipal waste	Philadelphia, Pa.	d(voa)	d(voa)	d(voa)	
Raw water contam. with municipal waste	Cincinnati, Ohio		d(voa)		
Raw water contam. with indust. discharge	Cincinnati, Ohio	d(voa)	d(voa)		
Raw water contam. with indust. discharge	Lawrence, Mass.		d(voa)		
Industrial discharge	Lawson's Fork Creek, N.C.				32,12(fid)
Industrial discharge	Catawba River	690(fid)			33(fid)
Industrial waste holding	Kentucky	15(ecd)			0.9(ecd)
Ground water	Kentucky	1.2, 71(ecd)			1.2,12(ecd)
Industrial discharge	Big Bigby Creek, Tenn.	40(fid)		58(fid)	
Submarine outfall, sew. treatment effluent	Point Loma, Calif.	<.01, 2.2		0.42, 1	
Submarine outfall, sew. treatment effluent	Oxnard, Calif.	4.7, 2.3		9.3,3.1	
Submarine outfall, sew treatment effluent	Joint Wat. Plant, So. Calif.	5.1(ec) 3.3(ms) 7.3, 12		7.6(ec) 7.4(ms) 7.4, 12	
Submarine outfall, sew. treatment effluent	Orange Co. Sew. Dep.	1.3(ec) 2.4		2.8(ec) 4.9	
Submarine outfall, sew. treatment effluent (5 miles)	Hyperion Sew. Treat. Works, Los Angeles, Calif.	1.9, 4		3.4, 5.1	
Submarine outfall, sew. (7 miles) effluent	Los Angeles River	183(ec) 14(ms) 30, 440		90(ec) 7.8(ms) 34, 230	

Table 2. - Dichlorobenzenes in raw and discharge waters[†] (Continued)

Medium or Sample	Location	1,2-DCB	1,3-DCB	1,4-DCB	DCB
River, rec. surface runoff after storm (4 day period)	Los Angeles River	0.01		0.05	
Chemical plant wastewater (seepage and cooling)	Michigan				10
Textile waste effluents	U.S.			detected	

[†]In mg x 10^{-3}/l; (cce) = carb. chlorof. extract; (voa) = vol. org. anal.; (ecd) = elect. conduct. detect. (fid) = flame ioniz. det.; (ec) = electron capt.,; (ms) = mass spec.

Table 3. - Dichlorobenzenes in U.S. drinking waters, mg x 10^{-3}/l

	ODBC	MDBC	PDCB	Reference
Highest concentrations reported as of 1975	1	<3	1	U.S. EPA, 1975
National Organics Reconnaisance Survey				
Miami, Fla.	1	0.5	0.5	U.S. EPA, 1975
Philadelphia, Pa.	d[A]	d	d	
Cincinnati, Oh.	d	d	d	
Lawrence, Mass.		d	d	

Concentrations reported in U.S. EPA's NOMS study during 1976 and 1977	Phase[†] II	III	Phase II	III	I	Phase II	III	Reference
No. pos./no. anal.	0/113	4/110	0/113	2/110	2/111	20/113	29/110	
Mean of pos. analyses, µg/l	--	2.5	--	0.10	2.0	0.14	0.07	
Median, all results, µg/l	<.005	<.005	<.005	<.005	<1	<.005	<.005	U.S. EPA, 1978a

[A] d=detected but not quantified.

[†] Phase I: samples shipped and stored at 2 to 8°c for 1 to 2 weeks prior to analyses; Phase II: samples held at 20 to 25°C for 3 to 6 weeks prior to analyses permitting reactions to proceed to end points (terminal values); Phase III: Samples processed with or without chlorine reducing agent - in these data, samples were processed without quenching additive, so were permitted to react to terminal values.

of chlorine treatment of secondary municipal wastewater effluents. Total organic-bound chlorine (TOCl) levels in concentrated extracts of effluents increased significantly after chlorination. Some of the aromatic halides identified were chlorobenzenes. Kopperman, et al. (1976) reported higher levels of chlorinated organic compounds (including dichlorobenzenes) in fish exposed (90 days) to chlorinated wastewater treatment plant effluent than in those exposed to nondisinfected effluent. They interpreted their data as indicating that even gentle chlorination conditions cause chlorine to be incorporated into organic molecules. Gaffney (1976) studied removal and formation of organic compounds at waste treatment plants processing waters containing effluents from textile processing plants. His data indicated that chlorinated components were formed by chlorination in the disinfection process at the treatment plant. In water purification plant samples the concentration of DCB's tended to increase in a downstream pattern. In two case studies the concentration of DCB in finished water was higher than in the raw water supply.

AIR

Data on air contamination by DCB's are very limited, but they suggest the potential for inhalation exposure. Dichlorobenzenes were measured in aerial fallout and high-volume samples taken at various locations in the Los Angeles area (Ware and West, 1977, citing Young, et al. 1976). Fallout samples were obtained at El Segundo, Catalina Island, San Clemente Island, La Jolla, and Santa Barbara. Levels of 1,2-DCB were reported as less than 8, 27, and less than 53 ng/m^2 ($mg \times 10^{-6}/m^2$) for Catalina Island, San Clemente, and Santa Barbara, respectively. Apparently no 1,4-DCB was detected in

fallout samples from any of the sites. DDT, Aroclor 1254, and Aroclor 1242 were present in samples from all sites and at levels much greater than for DCB. High-volume air samples were collected at the El Segundo, Catalina Island, and San Clemente sites. The 1,2-DCB level in air at El Segundo (estimated from reported filter analytic values at approximately 0.3×10^{-6} mg/m^3) was higher than that at Catalina Island and at San Clemente (similarly estimated at approximately 0.04×10^{-6} and $< 0.002 \times 10^{-6}$ mg/m^3, respectively). 1,2-DCB concentrations were considerably lower than for DDT and Aroclor 1254 at all sites. Data for 1,4-DCB were inadequate because of high and variable values in the analytical process blanks. The authors concluded that aerial fallout of chlorinated benzenes is less significant than that of DDT and PCB's because of the higher volatility of chlorinated benzenes. Gas-phase concentrations of DCB's were not reported.

Morita and Ohi (1975) have reported "appreciable" levels of 1,4-DCB in indoor and ambient air in and around Tokyo. The results of their survey of air contamination levels are summarized in Table 4. 1,4-DCB concentrations of 2.7 to 4.2 mg $\times 10^{-3}/m^3$ ($\mu g/m^3$) were measured outdoors in central Tokyo. In the outdoor atmosphere of suburban Tokyo levels of 1.5 to 2.4 mg $\times 10^{-3}/m^3$ were obtained. Considerably higher levels (0.105 to 1.7 mg/m^3) were measured in samples of indoor air (bedroom, closet, wardrobe). 1,4-DCB was also measured in human adipose tissue of residents. Morita and Ohi (1975) collected their airborne 1,4-DCB in the vapor phase by use of cold solvent traps, whereas Young, et al. (1976) collected their DCB from the particulate fraction of air in southern California using filter and fallout samplers.

The much higher airborne concentrations reported by Morita and Ohi may reflect that their Tokyo downtown and suburban air was more contaminated than the air at the California sites and/or that DCB is present in ambient air more as vapor than as a component of suspended particulates. In New Orleans, although all DCB isomers were detected in human blood samples in the area of New Orleans, no DCB's were detected in air or drinking water samples (Ware and West, 1977, citing Dowty, et al. 1975). The source of DCB's in the blood was not determined.

Table 4. - Atmospheric concentrations of 1,4-dichlorobenzene in and around Tokyo (Morita and Ohi, 1975)

Area		Concentration of 1,4-DCB ($mg \times 10^{-3}/m^3$)
Outdoors		
Central Tokyo	a. Residential	4.2
	b. Busy station square	2.7
	c. Main street	2.9
Suburbs	a. Quiet lake, 50 km west	1.5
	b. Major highway, 30 km west	2.4
	c. Farm, 15 km northwest	2.1
Indoors	a. Inside wardrobe	1,700
	b. Inside closet	315
	c. Bedroom	105

DCB contamination may exist in certain workplace atmospheres at much higher concentrations than exist in ambient air, presenting a greater exposure to persons in some occupations than to the general public. In workplace atmospheres associated with the manufacture of 1,4-DCB, Pagnotto and Walkley (1965)(cited by Ware and West, 1977) measured 1,4-DCB at air con-

centrations averaging 204 mg/m^3 (range: 42 to 288 mg/m^3) near washing of crystals, 198 mg/m^3 (range: 60 to 294 mg/m^3) near shoveling and centrifuging, and 150 mg/m^3 (range: 108 to 204 mg/m^3) during pulverizing, packaging. No concentrations of less than 48 mg/m^3 were found.

In the late 1930's a survey of fulling operations in three mills of the woolen industry using 1,2-DCB as a solvent, vapor concentrations in eight samples of workroom air ranged from 60 to 1,620 mg/m^3 (Hollingsworth, et al. 1958, citing Mass. Div. Occup. Hyg., 1937). Concentrations of 1,4-DCB were determined in samples of workplace air associated with manufacture and/or handling of 1,4-DCB (Hollingsworth, et al. 1956). In the 62 samples of the first survey concentrations of 1,4-DCB ranged from 60 to 3,300 mg/m^3 (average, 510 mg/m^3). In the second survey 15 samples collected under recurrent, severe, unpleasant work conditions ranged from 600 to 4,350 mg/m^3 (average 2,280), and 32 samples obtained during operations under "acceptable" conditions ranged from 30 to 1,650 mg/m^3 (average 540). In the third survey, after plant operating and equipment revisions, concentrations ranged from 300 to 1,020 mg/m^3 (average 630) in 21 samples collected under conditions associated with worker complaints (eye and nasal irritation). In 25 other samples, collected under no-complaint conditions, concentrations ranged from 90 to 510 mg/m^3 (average 270).

Novokovskaya, et al. (1976) reported 1,2-DCB as being among several organic compounds in gaseous emissions from the production of silicone medical tubing. 2,4-dichlorobenzene peroxide was an ingredient of resins

used in the manufacture. Emission gases were said to be below the maximum admissible concentrations (MAC). The recommended MAC for 1,2-DCB in the Soviet Union as of 1970 was 20 mg/m^3 (Int. Agency Res. Cancer (IARC), 1974).

FOOD

Dichlorobenzenes may be present in food commodities as a result of direct or indirect contamination from proper or improper uses or accidents. Schmidt (1971) reported the tainting of pork (disagreeable odor and tastes) as a result of the use in pig stalls of an odor-control product containing 1,4-DCB. Tainting of eggs was reported by Langner and Hilliger (1971) to result within 3 days from the exposure of hens to 1,4-DCB concentrations that did not affect the hens or egg production. Concentrations ranged from 20 to 38 mg/m^3. Morita, et al. (1975) reported detectable levels of 1,4-DCB in fish of the Japanese coastal waters. A species of mackerel (Trachurus trachurus) contained 0.05 mg/kg (wet weight). These authors also reported analyzing 1,4-DCB in human adipose tissue (obtained from central Tokyo hospitals and medical examiners' offices).

Dichlorobenzenes may occur in plant tissues as products of lindane or other chemicals' degradation. A DCB was found among several other polychlorinated benzenes constituting a nonpolar group of metabolites of lindane used on lettuce and endives (Kohli, et al. 1976). DCB's were recovered as lindane metabolites in roots of wheat plants grown from lindane-treated seed (Balba and Saha, 1974). 1,3-DCB was reported to be among several metabolites of gamma-pentachloro-1-cyclohexane in corn and pea seedlings (Mostafa and

Moza, 1973). There are not enough data to state quantitatively the degree of DCB exposure through total diet. Available evidence indicates that degree of environmental contamination by DCB's as a result of lindane degradation is probably very small (Ware and West, 1977). 1,2- and/or 1,4-DCB have also been measured in soils as products of lindane degradation (Mathur and Saha, 1977).

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured steady-state bioconcentration factor of 89 was obtained for 1,2-dichlorobenzene using bluegills containing about 1 percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus , the weighted average bioconcentration factor for 1,2-dichlorobenzene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 89 x 2.3 = 200.

A measured steady-state bioconcentration factor of 66 was obtained for 1,3-dichlorobenzene using bluegills containing about 1 percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 1,3-dichlorobenzene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 66 x 2.3 = 150.

A measured steady-state bioconcentration factor of 60 was obtained for 1,4-dichlorobenzene using bluegills containing about 1 percent lipids (U.S. EPA, 1978). An adjustment factor of 2.3/1.0 = 2.3 can be used to adjust the measured BCF from the 1.0 percent lipids of the bluegill to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 1,4-dichlorobenzene and the edible portion of all aquatic organisms consumed by Americans is calculated to be 60 x 2.3 = 140.

PHARMACOKINETICS

The dichlorobenzenes may be absorbed through the lungs, gastrointestinal (GI) tract, and intact skin. Relatively low water solubility and high lipid solubility of halobenzenes favor their penetration of most membranes by diffusion, including pulmonary and GI epithelia, brain, hepatic parenchyma, renal tubules, and placenta (Ware and West, 1977).

From their investigation of atmospheric contamination by 1,4-DCB in the Tokyo area (see Table 4), Morita and Chi (1975) suggested that inhalation is a major mode of human exposure to environmental 1,4-DCB. The same authors (Morita, et al. 1975) reported finding 1,4-DCB in all samples of human adipose tissue examined. In 32 samples obtained from local hospitals and medical examiners, representing subjects of both sexes and ages of 13 to 80 years, 1,4-DCB was measured at concentrations of 0.2 to 11.7 mg/kg (mean, 2.3). The mean concentration in adipose tissue was 246 times the mean concentration (9.3×10^{-3} mg/l) measured in six samples of whole blood representing males and females aged 21 to 35 years. Although 1,4-DCB was also measured at 0.05 and 0.012 mg/kg in samples of fish of the Japanese coastal waters, no concentrations were reported for other food items or for drinking water, so the relative contribution to body burden of 1,4-DCB by various exposure sources and routes is not clear. Nevertheless, even more than this body burden in Tokyo citizens' adipose tissue (2.3 mg/kg) could be accounted for entirely by inhalation exposure and pulmonary absorption if one assumed exposure to the higher airborne levels (mean, 0.707 mg/m^3) in indoor air (Morita and Chi, 1975) for most of the day, a body weight of 70 kg and an inspired volume of 23 m^3/day for the reference adult male (ICRP, 1975, cited by Natl. Acad. Sci. (NAS) 1978), an absorption efficiency of 50 percent by inhalation, and a bioconcentration factor of 60 (U.S. EPA, 1978c). Under such exposure conditions and assumptions an adipose tissue concentration (C) in the subject at equilibrium with environmental levels can be calculated as follows:

$$\frac{C = (0.707 \text{ mg/m}^3)(23 \text{m}^3/\text{day})(0.5)(60)}{70} = 6.97 \text{ mg/kg}$$

Thus, although the relative contribution to body burden by the respiratory route for the general public is probably less than indicated by this example, since the air levels to which they're exposed would likely be less than the high levels used in the calculation or they would not be exposed full time to the higher levels, the example implies that pulmonary absorption from airborne contamination by 1,4-DCB may be significant.

Inhalation of DCB vapors was primarily responsible for most (16 of 22) of a series of clinical cases of poisoning reported in the literature (Girard, et al. 1969; Sumers, et al. 1952; Weller and Crellin, 1953; Perrin, 1941; Cotter, 1953; Gadrat, et al. 1962; Petit and Champeix, 1948; Malbandian and Pierce, 1965; Campbell and Davidson, 1970; Downing, 1939; Frank and Cohen, 1961; Ware and West, 1977, citing: Dupont, 1938, and Wallgren, 1953). 1,2-DCB was the principal or a significant ingredient in five of these case reports and 1,4-DCB was similarly involved in eleven. Of these 16 cases, ten were occupationally related.

There were no data on the quantitative efficiency of absorption of DCB's via the respiratory route. However, Pagnatto and Walkley (1966) have measured urinary excretion of the principal DCB metabolite in occupationally exposed (by inhalation) persons and reported excretion occurred "soon after exposure ....began and peaked....at the end of the working shift," indicating that respiratory absorption during inhalation exposure is rapid.

Dichlorobenzenes, as well as other chlorinated benzene derivatives, may

be absorbed through the gastrointestinal tract. Lower halogenobenzenes are more readily and rapidly absorbed by this route than the higher homologues (Ware and West, 1977; Rimington and Ziegler, 1963). Three of the 22 cases of human DCB poisoning mentioned above resulted from accidentally or deliberately ingesting 1,4-DCB (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell, 1959). These cases clearly indicate significant absorption by the gastrointestinal (GI) route. Data on quantitative absorption efficiency of DCB's were sparse. Azouz, et al. (1955) detected no 1,4-DCB in feces of rabbits dosed intragastrically with the compound in oil. This suggests virtually complete absorption at least under their conditions. Animal experiments indicate that GI absorption of DCB's occurs and is fairly rapid, since metabolites, effects, and excretion have been observed within one day of oral dosing (Rimington and Ziegler, 1963; Azouz, et al. 1953; Poland, et al. 1971). 1,2-DCB and other components of Rhine River water contamination fed to rats at less than 0.4 to 2 mg/kg/day were absorbed and accumulated in various tissues indicating significant absorption by the GI tract even at low levels of exposure by ingestion (Jacobs, et al. 1974a,b).

Evidence in the literature indicates that DCB's are also absorbed via the skin (Ware and West, 1977). Three of the 21 clinical case reports mentioned previously involved dermal exposure and consequent toxicosis (Girard, et al. 1969; Downing, 1939; Nalbandian and Pierce, 1965). Reidel (1941) reported absorption of 1,2-DCB through the skin of rats in lethal amounts after 5 dermal applications under severe test conditions (painting twice daily directly on a 10 cm^2 area of abdominal skin) (Ware and West, 1977).

There were no data available on the quantitative efficiency of absorption by the dermal route in man or animals.

As noted previously, the relative insolubility in water and high lipid solubility of DCB's render them able to cross barrier membranes (Ware and West, 1977). This indicates that they (DCB's) would be widely distributed to various tissues. Clinical and experimental data also indicate wide distribution of these compounds to tissues. Lipid soluble halobenzenes tend to accumulate in the body, may reach toxic levels, and may recirculate for long periods. The tendency for cumulative effects is greater as the number of halogen substitutions on the benzene ring increases, but other influential factors include lipid solubility, the halogen substituent, the extent and nature of metabolism, the vapor pressure, and presence or absence of vicinal positions (Ware and West, 1977).

Human cases of poisoning and animal experimental toxicology and metabolism demonstrating changes in blood, blood chemistry, neuromuscular function, liver and kidney structure and function, and bone marrow elements indicate distribution of absorbed DCB's in and by blood to at least the brain, heart, liver, kidney, and bone marrow in multiple mammalian species (Hollingsworth, et al. 1956 and 1958; Ito, et al. 1973; Totaro and Licari, 1964; Totaro, 1961; Salamone and Coppola, 1960; Coppola, et al. 1963; Rimington and Ziegler, 1963; Azouz, et al. 1953, 1955; Poland, et al. 1971; Girard, et al. 1969; Sumers, et al. 1952; Cotter, 1953; Campbell and Davidson, 1970; Frank and Cohen, 1961; Petit and Champeix, 1948; Wallgren, 1953).

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In a study by Jacobs, et al. (1974a) 1,2-DCB and other chemicals known to be contaminants in Rhine River water were fed daily in a mixture to rats at 2 mg/kg (each component). Tissue accumulation was greater in fat than in the liver, kidney, heart, and blood. The same investigators (Jacobs, et al. 1974b) fed such a contaminant mixture to rats at two lower dose levels (0.4 and 0.8 mg/day) for 4 to 12 weeks. A dose-related accumulation of all compounds (including 1,2-DCB) in abdominal and renal adipose tissue occurred, and there was no evidence of saturation. The studies of Morita and Ohi (1975) and Morita, et al. (1975) have shown 1,4-DCB in adipose tissue (mean about 2 mg/kg) and blood (about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

Injection of DCB intramuscularly into hens at about 50 mg/kg resulted in recovery of 0.4 to 0.6 percent of the dose from yolks of eggs. The egg white contained negligible amounts. An increase in the chlorine content of chlorinated benzenes increased the period from injection to accumulation of residue in the yolk (Kazama, et al. 1972). DCB, as a metabolic residue of DDT injected intraperitoneally into mice during pregnancy, was found in fetal and maternal blood, brain, liver, and fat (Schmidt and Dedek, 1972).

Metabolism of the 1,2- and 1,4-DCB's was studied by Azouz, et al. (1955) in chinchilla rabbits. Single doses of 500 mg compound/kg body weight were given by stomach tube, the 1,2-DCB suspended in water and the 1,4-DCB dissolved in olive oil at 25 percent (w/v). Their results showed 1,2-DCB to be mainly metabolized by oxidation to 3,4-dichlorophenol and

excreted (primarily in urine) as conjugates of glucuronic and sulphuric acids. Peak excretion of these occurred on the first day after dosing Minor metabolites also formed and excreted as conjugates included 2,3-dichlorophenol (peak excretion on second day), 4,5-dichlorocatechol, 3,4-dichlorocatechol, and 3,4-dichlorophenylmercapturic acid. Metabolism and urinary excretion of 1,2-DCB was considered relatively slow, being essentially complete five to six days after dosing. During this period an average of 76 percent of the dose was excreted as "total conjugates," of which identified components were 48 percent glucuronide, 21 percent ethereal sulfate, and five percent mercapturic acid. 1,4-DCB was metabolized mainly by oxidation to 2,5-dichlorophenol and excreted as only glucuronides and ethereal sulfates. Peak excretions occurred on the second day after dosing, possibly reflecting a slower absorption (however, no 1,4-DCB was detected in the feces during the 6-day test period, indicating that absorption was essentially complete). 2,5-Dichloroquinol was also formed as a minor metabolite (about 6 percent of the dose), but in contrast to the case with 1,2-DCB, no mercapturic acid or dichlorocatechol was formed from 1,4-DCB. Total conjugates (64 percent of dose) during the 6-day period after dosing were comprised essentially of glucuronide (36 percent) and ethereal sulfate (27 percent), but excretion of metabolites was not considered complete after six days. Pagnatto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4-DCB in humans, and that levels excreted in urine were useful in assessing occupational exposure by inhalation.

Parke and Williams (1955) studied the metabolism and excretion of 1,3-DCB using the rabbit and methods as described by Azouz, et al. (1955), discussed above. An average of 54 percent of the administered dose of 1,3-DCB was measured as urinary conjugates of the metabolites, primarily glucuronides (36 percent) and ethereal sulfates (seven percent) which reach peak excretion on the first day after dosing. The major metabolite of 1,3-DCB was shown to be 2,4-dichlorophenol, accounting for at least 20 percent of the dose. 3,5-Dichlorophenol, 2,4-dichlorophenylmercapturic acid, and 3,5-dichlorocatechol were additional, minor metabolites. Excretion of 1,3-DCB was considered to be relatively slow, as with 1,2- and 1,4-DCB. Metabolites in measurable quantities were not excreted after 5 days from dosing, at which time about half of the dose was accountable for as total conjugates.

The detailed analytic and metabolic chemistries involved in the above studies are omitted here but are discussed in the original reports (Azouz, et al. 1955; Parke and Williams, 1955).

Daily dosing of rats with DCB's at doses of 450 to 1,000 mg/kg has induced ALA synthetase activity in liver and has produced hepatic porphyria characterized by increased levels of porphyrins and porphyrin precursors in liver and urine (Rimington and Ziegler, 1963; Poland, et al. 1971). Dosing with 1,3-DCB at 1000 mg/kg was porphyrogenic, but at 800 mg/kg a biphasic influence on hepatic metabolic activity was noted. There was an initial stimulation of ALA synthetase activity and increased urinary excretion of coproporphyrin, peaking at one and three days, respectively, and then a decline.

There was also a stimulation of drug metabolism by the hepatic microsomal system that peaked at five days. The investigators (Poland, et al. 1971) point out that porphyria could be caused in some cases by the 1,3-DCB or its metabolites (primarily 2,4-dichlorophenol in rabbits), but 2,4-DCP was not found in significant quantity in their animals (rats) so they felt that the 1,3-DCB was responsible in this experiment. They interpreted their decline in porphyria as probably being a result of the 1,3-DCB stimulating its own metabolism. A similar biphasic pattern of coproporphyrin excretion was observed in rats dosed with 2,4-DCP (the major metabolite of 1,3-DCB) and 1,4-DCB at 900 mg/k_g/day. Carlson and Tardiff (1976) also reported on the induction of hepatic microsomal xenobiotic metabolism systems by a DCB and other chlorinated benzenes. Chronic dosing of 1,4-DCB at low levels (10 to 40 mg/kg/day) in male rats increased detoxication of EPN (O-ethyl-o-p-nitrophenyl phenylphosphonothioate) benzpyrene hydroxylation and azoreductase activity (Ware and West, 1977). Effects persisted for at least 30 days after termination of exposure. The ability of halogenated aromatic compounds such as DCB's to induce enzyme systems associated with the metabolism of foreign compounds may influence the metabolism (and effects) of endogenous steroids, drugs, and foreign compounds (e.g., other environmental contaminants) (Ware and West, 1977).

Excretion of the metabolic products of the DCB's, primarily through the urine, is rather slow, as noted above. Five to six days were required to metabolize and eliminate the metabolites of a single intragastric dose (300 mg/kg) of 1,2- or 1,3-DCB. Elimination of the metabolites of 1,4-DCB (similar

dose) were not yet complete at six days after dosing (Parke and Williams, 1955), although this may have been influenced by a slower or delayed absorption. The excretion of DCB metabolites in rabbits dosed (single, intragastric) at 500 mg/kg body weight, as reported by Parke and Williams (1955) is summarized in Table 5. Peak excretion for some of the metabolites occurred on the first day after dosing and for others, later. Measurements by Pagnatto and Walkley (1966) of urinary dichlorophenol in workers exposed to 1,4-DCB indicated that excretion of metabolites began within the workshift "soon after exposure began," peaked at the end of the working shift, then decreased rapidly at first and then more slowly, continuing for several days.

Table 5. - Excretion of DCB metabolites by rabbits (Parke and Williams, 1955)*

Metabolite	1,2-DCB	1,3-DCB	1,4-DCB
Glucuronide	48	36	36
Ethereal sulfate	21	7	27
Mercapturic acid	5	11	0
Total conjugates	74	51	63
Monophenols	39	25	35
Catechols	4	3	0
Quinols	0	0	6
Period of excretion, days	6+	5+	6**

*Data expressed as percent of dose fed (500 mg/kg).

+Excretion apparently complete

**Excretion not complete.

Ware and West (1977) stated that the portion of halogenated benzenes that escape biotransformation "may be excreted in part unchanged in the urine, feces, or expired air." No information was available to quantify these phenomena. These authors also indicated that halogenobenzenes which are not extensively metabolized: (1) may be hazardous if they form an arene oxide intermediate; (2) not only tend to accumulate in the body to reach toxic levels but may recirculate for long periods; and (3) toxic intermediates (e.g., arene oxides, phenols) resulting from metabolism may cause repeated tissue insults and increase the likelihood of cellular damage. Azouz, et al. (1955) and Parke and Williams (1955) did not report any excretion by way of the feces, nor did they report the fate of that portion of administered DCB's not accountable for by the urinary metabolites. Available data also did not provide information on the efficiency of detoxication and elimination of the DCB's in humans at lower, more "realistic" environmental levels. Half-lives of less than one day were reported for DCB's in tissues of fish (bluegill sunfish, Lepomis macrochirus) (U.S. EPA, 1978c).

As noted previously, nonmetabolized DCB's accumulate in tissues. Bioconcentration factors in fish (bluegill sunfish) were reported as 39, 66, and 60 for 1,2-, 1,3-, and 1,4-DCB, respectively (U.S. EPA, 1978c). Morita and Ohi (1975) reported levels averaging about 2 mg/kg in adipose tissues of residents of the Tokyo area compared with blood levels averaging only 0.0095 mg/l. When several Rhine River contaminants including 1,2-DCB were fed to rats, tissue accumulation was greater in fat tissue than in liver, kidney, heart, and blood, and there was no evidence of saturation (at dose levels of

less than 1 mg/day)(Jacobs, et al. 1974a,b). Residue of DCB in eggs of injected (intramuscularly) hens was measured at much higher levels in the yolk sac than in white (about 0.5 percent of dose vs. virtually none)(Lunde and Ofstad, 1976). Eggs of hens exposed to 1,4-DCB in air at 20 or 38 mg/m^3 developed an unpleasant taste within three days, and two metabolites were detected in the yolks (Langner and Hilliger, 1971). Undesirable odor and taste of pork meat from swine exposed to vapors of 1,4-DCB used for odor control in the stalls were reported by Schmidt (1971).

EFFECTS

Toxicity

Prior to the 1940's very little had been reported concerning any harmful properties of DCB's, which had become industrially important in recent years, and they were generally regarded as having no, or very low, toxicity for man (Downing, 1939; Perrin, 1941). However, clinical data reported beginning in 1939 have substantiated the conclusion that DCB's should no longer be considered harmless (Perrin, 1941).

Most reported cases (16 of 22) of human poisoning by DCB's since 1939 have resulted from long term exposure primarily by inhalation of vapors, but some have also resulted from exposure by ingestion (3 of 22) and skin absorption (3 of 22). Toxic exposures have been occupational in nature in most cases, but have also involved the use or misuse of DCB products in the home.

Most case reports (15 of 22) have involved exposure to agents containing primarily 1,4-DCB, and the remainder involved primarily 1,2-DCB. In some of these, DCB mixtures including 1,3-DCB were involved. Target systems or tissues have involved one or more of the following: liver, blood (or reticuloendothelial system, including bone marrow and/or immune components), central nervous system (CNS), respiratory tract, integument (Dupont, 1938; Girard, et al. 1969; Gadrat, et al. 1962; Downing, 1939; Sumers, et al. 1952; Cotter, 1953; Petit and Champeix, 1948; Perrin, 1941; Weller and Crellin, 1953; Hallowell, 1959; Campbell and Davidson, 1970; Frank and Cohen, 1961; Nalbandian and Pierce, 1965; Ware and West, 1977, citing Wallgren, 1953).

Clinical findings in these reports, which are summarized in Table 6, imply broad toxicologic propensities for the DCB's in terms of biological systems and tissues affected. For example, at least 17 of the 22 reported clinical cases have involved general toxic or irritative symptoms (e.g., fatigue or weakness, anorexia, weight loss, nausea, headache, irritation, malaise); at least 17 have involved symptoms or signs relative to involvement of the circulatory system including blood and/or bone marrow or other reticuloendothelial components (e.g., anemia, leukemia, leukopenia or leukocytosis, polynucleosis, bone marrow hyperplasia, leukoblastosis, hemorrhagic tendency, splenomegaly, jaundice); at least six have involved damage to the liver (e.g., hepatomegaly, subacute yellow atrophy, cirrhosis); at least three have involved the skin (e.g., irritation, fixed drug eruption, purpura); one to three have involved allergy or sensitization (allergic purpura, eczematoid dermatitis); one or two have involved the respiratory system or

Table 6. - Human poisoning by dichlorobenzene

Compound	Subjects and exposure	Effects	Reference
1,2-DCB (vapor)	Sewage workers; occupational; inhalation; effluent from dry cleaning establishment.	Eye and upper respiratory tract irritation, vomiting.	Dupont, 1938
1,2-DCB solvent mixture: 80% 1,2-DCB; 15% 1,4-DCB; 2% 1,3-DCB.	Male, 40 yrs; occupational; use of solvent to clean equipment; chronic daily exposure probably inhalation of vapor, and perhaps dermal absorption from clothing.	Weakness, fatigue; peripheral lymphadenopathy; chronic lymphoid leukemia.	Girard, et al. 1969.
1,2-DCB solvent mixture: 95% 1,2-DCB; 5% 1,4-DCB	Female, 18 yrs; occupational; chronic daily inhalation exposure to vapors as pressing-ironing worker.	Severe acute hemolytic anemia; leukocytosis; polynucleosis; fatigue, nausea, headache; icterus; bone marrow hyperplasia; possible inherent predisposing factor.	Gadrat, et al. 1962
1,2-DCB and other chlorobenzene	Male, 60 yrs; occupational; filling barrels with 1,2-DCB and other chlor. benzenes (mono-, tri-); chronic inhalation of vapors (last 3 years), perhaps also skin contact.	Anemia, requiring transfer to other work.	Girard, et al. 1969
1,2-DCB included in mixture	Male, 47 yrs; occupational; handling window sashes dipped in solution; chronic skin contact (also inhalation).	Contact eczematoid dermatitis (itch, eruption) on hands, arms, face; erythema, edema, bullae in response to skin test.	Downing, 1939
1,2-DCB (37% in commerc. soln.)	Female, 15 yrs; non-occupational; chronic repeated dermal contact from compulsive use of cleaning solution on clothing (in place)	Acute myeloblastic leukemia progressing to 100% leukoblastosis, hemorrhage, death.	Girard, et al. 1969

Table 6. - Human poisoning by dichlorobenzene - p.2

1,2-DCB 80% (in solvent mixture with 1,4-DCB, 15% and 1,3-DCB, 2%)	Female, 55 yrs; non-occupational; chronic repeated inhal. exposure to vapors from use of solution to clean clothes; 1 to 2 l/year.	Acute myeloblastic leukemia	Girard, et al. 1969
1,4-DCB primarily	Female, 30 yrs; occupational; for two years selling mothballs and insecticide products containing 1,4-DCB chiefly; chronic inhalation, perhaps some dermal component.	Weakness, nausea, splenomegaly; "severe hepatocellular derangement and ensuing portal hypertension" with esophageal varices.	Sumers, et al. 1952
1,4-DCB primarily	Female, 34 yrs; occupational; demonstrating 1,4-DCB products in booth in department store; odor strong in area; chronic exposure to vapors	Malaise, then acute nausea, vomiting, headache, icterus, hepatomegaly, splenomegaly; esophageal varices and hemorrhoids; subacute yellow atrophy and cirrhosis of liver.	Cotter, 1953
1,4-DCB	Male, 52 yrs; occupational; used 2 years in fur warehouse (formerly used naphthalene); chronic inhalation exposure to high vapor levels.	Weakness, nausea, hematemesis, jaundice, emaciation, petech. hemorrhages; hepatomegaly, splenomegaly, hemorrhoids; proteinuria, bilirubinuria; hematuria; anemia, leukopenia; subacute yellow atrophy of liver.	Cotter, 1953
1,4-DCB primarily	Female, 19 yrs; occupational; crushing, pouring, sieving, filling containers; poor ventilation; chronic inhalation of vapors.	Marked asthenia, dizziness, weight loss; anemia and reactional leucocytosis.	Petit and Champeix, 1948
1,4-DCB	Female; occupational; casting 1,4-DCB in molds; chronic inhalation (skin contribution unknown, if any)	Severe anemia	Perrin, 1941

Table 6. - Human poisoning by dichlorobenzene - p. 3

1,4-DCB	Male, 20 yrs. and workmates; occupational; 1,4-DCB manufacturing activities; 1 to 7 months exposure; inhalation (presumably).	Weight loss, exhaustion, decreased appetite; methemoglobinemia and other blood pathologies.	Wallgren, 1953 (cited by Ware and West, 1977).
1,4-DCB	Male, 62 yrs; nonoccupational; used "moth killer" product in bathroom at home; chronic inhalation of vapors, and wearing of impregnated clothing (possible skin exposure).	Asthenia, dizziness; anemia, hypogranulocytosis. Similar to cases of intoxication by benzene	Perrin, 1941
1,4-DCB	Female, 36 yrs; nonoccupational; use of commercial moth killer in home (presumably inhalation of vapors).	Acute illness with intense headache, profuse rhinitis, perforbital swelling.	Cotter, 1953
1,4-DCB	Male, 60 yrs; nonoccupational; 3 to 4 months exposure to "moth gas vapor" in home.	Headache, weight loss, diarrhea, numbness, clumsiness; icterus, enlarged liver, anemia, neutropenia; developed ascites, died; acute yellow atrophy of liver.	Cotter, 1953
1,4-DCB	Female, wife of above, nonoccupational; prolonged severe exposure to "moth gas vapor".	Gradual loss of strength and weight, then abdominal swelling and jaundice before acute illness; elevated temperature and pulse, dilated vessels, swollen liver, toxic granulocytosis; died 1 year later: acute yellow atrophy (liver), Laennec's cirrhosis, splenomegaly.	Cotter, 1953

Table 6. - Human poisoning by dichlorobenzene - p. 4

1,4-DCB	Female, 53 yrs; nonoccupational; used moth eradicator product heavily in home for 12 to 15 years, odor always apparent; chronic inhalation of vapor.	Chronic progressive cough and dyspnea with mucoid sputum, wheezing, fatigue; diminished breath sounds and rales; abnormal lung field on x-ray; fibrotic, rubbery lung with numerous granulomatous lesions and architecture changes on histology of biopsy; diagnosis: pulmonary granulomatosis.	Weller and Crellin, 1953
1,4-DCB	Male, 3 yrs; nonoccupational; played with canister of de-mothing crystals, spreading on floor, handling; ingestion, likely acute.	Listlessness, jaundice, oliguria, methemoglobinuria and other urine abnormalities, anemia, hypothermia; diagnosis: acute hemolytic anemia.	Hallowell, 1959
1,4-DCB	Female, 21 yrs; nonoccupational; ingestion during pregnancy of toilet air freshener blocks (pica) at rate of 1 to 2 each week.	Fatigue, anorexia, dizziness, edema of ankles; hypochromic microcytic anemia; bone marrow normoblastic hyperplasia; diagnosis: toxic hemolytic anemia. Recovery complete.	Campbell and Davidson, 1970.
1,4-DCB	Female, 19 yrs; nonoccupational; ingestion (pica), 4 to 5 moth pellets daily for 2 1/2 years.	Increased skin pigmentation in areas 3 to 7cm. diameter on limbs; mental sluggishness; tremor, unsteady gait upon withdrawal, along with decrease in pigmentation. Diagnosis: fixed drug eruption, conversion hysteria.	Frank and Cohen, 1961

Table 6. - Human poisoning by dichlorobenzene - p. 5

1,4-DCB	Male, 69 yrs; nonoccupational; dermal exposure, presumably interrupted; episode precipitated by use of chair treated with 1,4-DCB.	Dyspnea followed by stiff neck; "tightness" in chest, "gas pains" in abdomen; symmetrical petechia and purpura on extremities, swelling discomfort; stool occult blood positive, blood cells in urine, and incr. BUN; basophil degranul. test positive for 1,4-DCB; Diagnosis: allergic (anaphylactoid) purpura and acute glomerulonephritis.	Nalbandian and Pierce, 1965.

lungs (e.g. upper respiratory irritation, rhinitis, cough, pulmonary granulomatosis); two have involved CNS-related or neuromuscular signs or symptoms (e.g., numbness, clumsiness, tremor, unsteady gait, conversion hysteria); and one appeared to involve kidney damage, directly and/or indirectly (e.g., glomerulonephritis, oliguria, hematuria, urinary abnormalities).

Reidel (1941) reported that a burning sensation was produced when 1,2-DCB was applied for 15 minutes to the skin of human subjects. The response intensified with continued exposure up to one hour and abated when the liquid was removed. However, hyperemia and blisters developed at the site of application afterward, followed by a brown pigmentation that persisted at least three months (Hollingsworth, et al. 1958). Analyses of workroom air associated with 1,2-DCB manufacture and handling operations at the Dow Chemical Company were reported (Hollingsworth, et al. 1958) as ranging from 6 to 264 mg/m^3, with an average of 90 mg/m^3 (40 samples). Medical examinations of workers from time to time, including hemograms and urinalyses, revealed no evidence of organic injury or adverse hematologic effects attributable to 1,2-DCB exposure. Although Patty (1963) and Hollingsworth, et al. (1958) stated that eye and nose irritation are not noticeable at the concentration in air detectable by the average person (300 mg/m^3), the Am. Conf. Gov. Ind. Hyg. (ACGIH)(1977) mention that a ceiling limit of 300 mg/m^3 should prevent serious but not all eye and nose irritation. Elkins (1959) reported concentrations approaching 600 mg/m^3 to be irritating but without other effects (ACGIH, 1977).

Hollingsworth, et al. (1956) have reported on surveys of plant conditions associated with the manufacture of 1,4-DCB. Workroom air contamination levels were previously summarized in the section on exposure. Workers were monitored also under the various conditions of air contamination in the surveys. These data indicated that concentrations of 1,4-DCB greater than 960 mg/m^3 were irrespirable (intolerable) for unacclimated persons, painful irritation of the eyes and nose occurred at levels of 480 to 960 mg/m^3, odor was strong at 180 to 360 mg/m^3, and a faint odor was noticeable at 90 to 180 mg/m^3. Workers complained under conditions yielding air sample concentrations ranging from 700 to 1,020 mg/m^3, but conditions yielding samples with concentrations of 90 to 510 mg/m^3 did not elicit complaints. In the data of periodic medical examinations on the workers there was found no evidence of organic injury or adverse changes in hematology or eye lenses attributable to 1,4-DCB exposure (Hollingsworth, et al. 1956). Solid particles of 1,4-DCB and heavy vapors or fumes (such as when heated and volatalized in poorly ventilated spaces) are painful to the eyes and nose. The painful effect of vapors is evident to most people at 300 to 480 mg/m^3 and is severe at 960 mg/m^3 or more. Tolerance or acclimatization may occur with repeated exposure, so sensory warning properties may be less protective of more generalized toxicity in these persons (Hollingsworth, et al. 1956).

Solid 1,4-DCB is not regarded as signifcantly irritating to intact skin unless held in close contact for some time, when it may produce a burning sensation. Warm fumes or strong solutions may be irritating to skin on prolonged and repeated contact, but 1,4-DCB is said to produce no significant

hazard from skin irritation or absorption except under extreme conditions (Hollingsworth, et al. 1956).

Although Berliner (1939) reported two cases of human cataract he believed due to chronic exposure to a 1,4-DCB-containing moth or deodorant product, Hollingsworth et al. (1956) has interpreted considerable subsequent human data as indicating that 1,4-DCB does not produce human cataracts.

Varshavskaya (1967a) reported that odor and taste thresholds for 1,2-DCB in water were determined to be 0.002 and 0.0001 mg/l, and for 1,4-DCB, 0.002 and 0.006 mg/l, respectively. The olfactory and gustatory thresholds for DCB's were also separately reported as 0.001 to 0.002 mg/l (Varshavskaya, 1967b). These organoleptic properties have been considered in establishing Russian tolerance levels of 1,2- and 1,4-DCB in drinking water (Stofen, 1973).

The 1,2- and 1,3-DCB's are extensively metabolized. One theory for the mechanism of toxicity of DCB's (i.e., cellular damage) is that reactive metabolites such as arene oxides or epoxides are formed in the process of metabolic transformation of the parent foreign compound through the action of hepatic microsomal enzyme systems involving cytochrome P-450. The enzymes concerned with foreign compounds (including drugs), often referred to as mixed function oxidases (MFO), are located in the endoplasmic reticulum (ER) of liver cells and require nicotinamide adenine dinucleotide phosphate ($NADPH_2$), molecular oxygen, and P-450 (a cytochrome). Biotransformation of

drugs and other xenobiotic chemicals occurs in two phases: (1) oxidation, reduction, and hydrolysis reactions, and (2) syntheses or conjugations. Biotransformation enzymes and reactions vary among species and tissues and are influenced by steroids and the parent or other xenobiotics. P-450 and the ability to form toxic intermediate metabolites also vary with species. Other factors affecting biotransformation and xenobiotic toxicity are the quantity of enzymes catalyzing conjugation with glutathione (an important detoxification mechanism but also a mechanism of damage since glutathione depletion by such a process is associated with toxicity and cellular damage) and forming mercapturic acids, and the concentration of the enzyme epoxide hydrase (Ware and West, 1977, citing: Williams, 1959; Parke, 1968, 1972; Ahokas, et al. 1976; Gigon, et al. 1968; Reid, et al. 1973; Reid and Krishna, 1973).

When biotransformation of bromobenzenes (a prototype hepatotoxic chemical relative of DCB) is stimulated by pretreatment with phenobarbital (an MFO-inducer or stimulant) the hepatic damage in rats is enhanced. Conversely, blocking metabolism of the bromobenzene by use of SKF-525A or piperonyl butoxide (metabolic inhibitors) lessens the toxicity. Studies of halobenzenes have shown that toxicity such as reflected by hepatic necrosis is a result of their conversion to reactive toxic intermediate metabolites (Ware and West, 1977, citing: Brodie, et al. 1971; Reid, et al. 1971, 1973; Mitchell, et al. 1971; Reid and Krishna, 1973). In the case of bromobenzene, the hepatic necrosis results from the reaction of the toxic intermediate, arene oxide, with cellular macromolecules. Severity of hepatic

necrosis correlates well with the extent of covalent binding and with conjugation with glutathione (and the latter's consequent depletion)(Ware and West, 1977, citing: Reid, et al. 1973; Reid and Krishna, 1973).

Bromobenzene and 1,2-DCB caused hepatic necrosis in rats, significant covalent binding, mercapturic acid excretion, and glutathione depletion (Ware and West, 1977, citing: Reid, et al. 1971b; Reid, et al. 1973; Reid and Krishna, 1973).

In 1937 Cameron, et al. (1937) reported on early toxicity tests of 1,2-DCB. Some of the work used a mixture containing only 48.8 percent 1,2-DCB, so conclusions as to specific toxicity of the pure compound may be questionable. However, in one exposure of rats exposed 11 to 50 hours to pure 1,2-DCB vapor at 4,800 mg/m^3 (calculated), nasal and ocular irritation, drowsiness, coma, massive liver necrosis, and death (one in ten) were observed (Hollingsworth, et al. 1958; Ware and West, 1977).

Much later, Hollingsworth, et al. (1958) more exhaustively investigated the toxicity of 1,2-DCB using inhalation, gastric intubation, and ocular exposure techniques in several species of experimental animals and over a range of lower dose levels. In the inhalation studies groups of 20 rats, eight guinea pigs, four rabbits, and two monkeys were exposed to vapors seven hours per day, five days per week for six to seven months at an average concentration of 560 mg/m^3. On the basis of the following criteria, no adverse effects were noted in any of the species: gross appearance,

follows (in mg/kg body weight):

Species	1,2-DCB	1,4-DCB
White mice	2,000	3,220
White rats	2,138	2,512
Rabbits	1,875	2,812
Guinea pigs	3,375	7,593

The acute poisoning manifestations were similar between compounds and among species, and included: hyperemia of mucous membranes; increased lacrimation and salivation; excitation followed by sleepiness, adynamia, ataxia, paraparesis, paraplegia, and dyspnea developing into Kuss-Maul breathing; death due to central respiratory paralysis, usually within three days; autopsy findings of plethora of parenchymatous organs, enlarged liver with necrotic areas, submucosal hemorrhages in stomach, brain edema; histological findings of vascular and necrotic changes in the liver, stomach mucosa, and kidneys, and brain edema. In a follow-up experiment rats were given DCB's at a daily dose level of 1/5 of the LD_{50} dose. 1,2-DCB, in contrast to 1,4-DCB, was concluded to be a cumulative toxin since half of the animals died when they had received a total dose equal to the single LD_{50} dose. 1,4-DCB was, again, less toxic than 1,2-DCB.

In a chronic toxicity test rats were given 1,2-DCB at daily doses of 0.001, 0.01, and 0.1 mg/kg. Toxicity was evaluated on the basis of multiple criteria, including: weight; hematology; serum enzymes and protein fractions;

behavior, growth, organ weights, hematology (rabbits, monkeys), urinalysis (qualitative, for blood, sugar, albumin, sediment), blood urea nitrogen, gross and microscopic examination of tissues, mortality. A similar test using 20 rats, sixteen guinea pigs, and ten mice exposed to 290 mg/m^3 in the same pattern for six and one half months was also negative.

Hollingsworth, et al. (1958) conducted single- and repeated-oral-dose studies of 1,2-DCB. Intubation of 10 guinea pigs with 1,2-DCB (50 percent in olive oil) in single oral doses of 800 mg/kg resulted in loss of body weight, but was survived by all subjects, whereas 2,000 mg/kg doses were fatal to all subjects. In a test of repeated doses of 1,2-DCB in olive oil emulsified with acacia, groups of white rats were dosed by stomach tube five days a week for a total of 138 doses in 192 days at dose levels of 18.8, 188, and 376 mg/kg. Positive toxicologic findings in the high-dose subjects included: increased liver and kidney weights, decreased spleen weight, and slight to moderate cloudy swelling on microscopic examination of the liver. In the intermediate-dose group liver and kidney weights were slightly increased. No adverse effects were noted at the low-dose level. Two drops of undiluted 1,2-DCB in rabbits' eyes caused pain and conjunctival irritation, which cleared completely within one week. Prompt washing with water reduced pain and irritation.

Varshavskaya (1967a) reported on the hygienic evaluation of dichlorobenzenes in reservoir waters. Median lethal dose (LD_{50}) values for DCB's given to four animal species in single doses in oil by stomach tube are as

prothrombin index; leukocyte phagocytosis; sulhydryl groups in blood; urinary 17-keto-steroids; conditioned reflex activity. Preliminary results reported as of five months into the experiment indicated that 1,2-DCB was toxic and exerted a predominant effect on the hematopoietic system. Effects included: reduced hemoglobin, erythrocytes, and thrombocytes; increased leukocytes and reticulocytes (an apparent shift of the blood formula to the left); increased prothrombin time and activity of alkaline phosphatase and transaminases; altered liver and central nervous system function; altered conditioned reflex activity (Varshavskaya, 1967a).

According to Varshavskaya (1967b), results after nine months, at completion of the chronic test, were interpreted as follows: At the 0.1 mg/kg dose level 1,2-DCB disturbed higher cortical function in the central nervous system; the 0.01 mg/kg dose level ws "liminal," and the low dose level (0.001 mg/kg) was "subliminal." The high level dose (0.1 mg/kg) caused inhibition of erythropoiesis (decreased hemoglobin and erythrocytes, anisocytosis, poikilocytosis, increased reticulocytes), thrombocytosis, neutropenia, and inhibited bone marrow mitotic activity. Similar but less pronounced effects were noted at the intermediate level, and the low dose level had no such effects. At the high dose level there was a marked increase in urinary 17-ketosteroids, with an increase in adrenal weight coefficient and decrease in adrenal ascorbic acid content. The high level resulted in increased alkaline phosphatase and serum transaminase activity, and decreased glutathione (SH) groups in blood; reduced alkaline phosphatase and increased acid phosphatase; and decreased di- and triphosphopyridinenucleotides in liver and

kidneys; decreased succinic dehydrogenase, glucose-6-phosphatase, and a-glycerophosphate in liver and kidney. The intermediate exposure had similar effects on blood enzymes and less effect on other enzyme activities. No enzyme-system effects were noted in the low-dose subjects. Although the 0.1 and 0.01 mg/kg regimens caused decreased alkaline phosphatase, there was no microscopic or histologic evidence of carcinogenic activity. The maximal innocuous concentration of 1,2-DCB in water by toxicological criteria was considered to be 0.02 mg/l (extrapolated from 0.001 mg/kg/day), and by water sanitation criteria 0.2 mg/l, but since the liminal concentration by organoleptic criteria (taste, odor) was 0.002 mg/l, the recommended maximum permissible water concentration was set at 0.002 mg/l. Although toxicity of 1,4-DCB was regarded as less than 1,2-DCB its organoleptic and sanitary properties were similar to those of 1,2-DCB, so its recommended maximum permissible concentration was set at 0.002 mg/l (as for 1,2-DCB) on the organoleptic basis (Varshavskaya, 1967b).

The toxicological observations of Varshavskaya (1967a,b) are in quite good qualitative agreement with the clinical toxicity of DCB's discussed earlier (e.g., anemia and other blood changes, liver damage, central nervous system depression) and with some aspects of other reported animal toxicology, but indicate that adverse effects occur at considerably lower exposure levels than indicated by the other data.

The highest no-detected-adverse-effect level for 1,2-DCB reported by Varshavskaya (1967b) was 0.001 mg/kg/day, whereas the comparable subliminal level in the longterm rat study by Hollingsworth, et al. (1957) was 18.8

mg/kg/day. The reason for this discrepancy of several thousand-fold is not clear.

Acute and subacute toxicity of 1,4-DCB was investigated by Ito, et al. (1973) using subcutaneous injections and inhalation test methods. Male mice (22-26g) were injected subcutaneously with 1,4-DCB in olive oil at doses ranging from 3,500 to 7,258 mg/kg and observed over one week. The calculated LD_{50} dose for 1,4-DCB was reported as 5,145 mg/kg (4,760 to 5,530). Tremor occurred within two to three hours and continued over three days. Naphthalene was more potent (LD_{50}, 969 mg/kg) but both were regarded as nerve toxins and death was attributed to respiratory paralysis. Mice were exposed to atmospheres containing 1,4-DCB vapors for one 8-hour period and for two weeks at eight hours per day. The 8-hour exposure caused "inertia" (probably lassitude, weakness, or listlessness) and an increased breathing rate. The subacute repeated exposure resulted in liver damage and a blood level of 6.5 mg 1,4-DCB/l. Vapor concentrations were not clearly identified in the translated report.

Hollingsworth, et al. (1956) reviewed some of the literature concerning toxicity of 1,4-DCB. The report of Landsteiner and Jacobs (1936) that the material did not sensitize guinea pigs' skin should be interpreted with caution in view of the clinical report of allergic purpura by Nalbandian and Pierce (1965). Berliner's report in 1939 of lenticular cataracts in humans exposed to vapors containing 1,4-DCB was not substantiated in subsequent studies with better identification of vapors or more controlled experimental

conditions (Hollingsworth, et al. 1956, citing: Pike, 1944; Zupko and Edwards, 1949; Ballotta and Mattiole, 1942; Teramoto, 1936). Further, 1,4-DCB does not produce mercapturic acid and interfere with lens metabolism (by virtue of inhibition and/or depletion of glutathione, cytaine, and protein), as does napthalene, which is cataractogenic.

Several species of laboratory animals were exposed to 1,4-DCB vapors at each of five concentrations for seven hours per day (eight for the highest dose group), five days per week (Hollingsworth, et al. 1956). Effects in animals (rats, guinea pigs, rabbits) exposed to 4,800 mg/m^3 for up to 69 exposures included: some deaths (up to 25 percent); marked tremors, weakness, collapse; eye irritation, and reversible eyeground changes in rabbits, but no lens changes in any; weight loss; liver degeneration and necrosis; cloudy swelling of renal tubular epithelium (rats); lung congestion and emphysema (rabbits). Effects in rats and guinea pigs exposed at a concentration of 2,050 mg/m^3 for six months included: growth depression (guinea pigs); increased liver and kidney weights (rats); liver pathology (cloudy swelling, fatty degeneration, focal necrosis, cirrhosis). Effects in animals exposed for up to 139 exposures over 199 days at 1,040 mg/m^3 were: increased liver, splaen, and kidney weights (guinea pigs); pulmonary edema, congestion, hemorrhage; hepatic centrolobular congestion and granular degeneration (rats). Effects in animals exposed at 950 mg/m^3 for 157 to 219 days included: growth depression (guinea pigs); increased liver weight (rats, guinea pigs) and kidney weight (rats); centrolobular hepatocellular cloudy swelling or granular degeneration (rats). Effects in animals exposed to 950

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mg/m^3 for 157 to 219 days included: growth depression (guinea pigs), increased liver weight (rats, guinea pigs) and kidney weight (rats); centrolobular hepatocellular cloudy swelling or granular degeneration (rats). No adverse effects were observed in rats, guinea pigs, rabbits, mice, and a monkey exposed at 580 mg/m^3 for six to seven months.

Results from acute, single, high-level exposures to 1,4-DCB in oil by stomach tube are summarized as follows:

Species	LD_0	LD_{100}
Rats	1,000 mg/kg	4,000 mg/kg
Guinea pigs	1,600 mg/kg	2,800 mg/kg

1,4-DCB was dissolved in oil and given to male adult rats at 10, 100, or 500 mg/kg/dose five days per week for four weeks. Cetrolobular hepatic necrosis and marked cloudy swelling of renal tubular epithelium with cast formation occurred in subjects exposed to 500 mg/kg. No effects were observed at the lower dose levels (Hollingsworth, et al. 1956).

White female rats were fed 1,4-DCB in oil (emulsified with acacia) by stomach tube five days a week for a total of 138 doses in 192 days (Hollingsworth, et al. 1956). At the high dosage level of 376 mg/kg/dose increased liver and kidney weights, and hepatic cirrhosis and focal necrosis were observed. At the intermediate dose level of 188 mg/kg/dose increased liver and kidney weights were observed. No adverse effects were noted at the low dose level (18.8 mg/kg). No cataracts were observed in these exposures. The same investigators fed rabbits with 1,4-DCB in oil by intubation for up to 92 doses in 219 days at a high level of 1,000 mg/kg/dose. Another group recieved

a dose level of 500 mg/kg/dose five days a week for a total of 263 doses in 367 days. Effects at the high dose level (1,000 mg/kg) included: weight loss, tremors, weakness, hepatic cloudy swelling and focal necrosis, deaths. Similar changes, but no deaths, were noted in rabbits on the lower dose regimen. No cataracts were observed. In Peking ducks fed 1,4-DCB in their diet at 0.5 percent (5,000 mg/kg diet) for 35 days retarded growth and 30 percent mortality in 28 days, but no cataracts, were observed (Hollingsworth, et al. 1956).

Coppola, et al (1963) reported an effect on blood coagulation (increase in thromboelastrogram reaction and clotting formation times) in guinea pigs injected intramuscularly with daily doses of 125 mg 1,4-DCB in oil for three weeks. Totaro (1961) reported weight loss and increased serum transaminases in guinea pigs injected intramuscularly with 1,4-DCB (50 percent in oil) for 11 and 20 days at 125 mg per day. The increase in the glutamic-oxalacetic transaminase (SGOT) level was greater than the increase in glutamic-pyruvic transaminase (SGPT). The level of serum aldolase was not altered. The effect of lipotropic factors on transaminase and weight loss effects of injected 1,4-DCB was later studied by Totaro and Licari (1964). Besides controls, groups of guinea pigs were injected intramuscularly daily for 20 days with 125 mg 1,4-DCB in oil (group 2), with a mixture of betaine chloride 70 mg: choline chloride 75 mg:Vitamin B_1 1 mg:Vitamin B_{12} 0.5 microgram (group 3), or with 125 mg 1,4-DCB together with the lipotropic mixture (group 4). Weight losses in groups 2 and 4 were 11.4 and 5.5 percent, respectively. SGOT and SGPT increases in group 2 were 312 and 149 percent, respectively and in group 4 they were, respectively, 187 and 124 percent. The authors concluded

that the lipotropic factors exerted a protective action on the enzymatic modifications induced by 1,4-DCB. A similar protective action by lipotropic factors against the lowering of clotting factors ascribed to liver damage by 1,4-DCB was demonstrated by Salamone and Coppola (1960) in an experiment similar to that just described for the transaminases.

Hepatic prophyria was induced in rats fed 1,2- and 1,4-DCB in liquid paraffin by stomach tube at levels increasing over several days to 455 and 770 mg/kg, respectively (Rimington and Ziegler, 1963). The first sign of intoxication was a markedly increased urinary excretion of urinary copro-porphyrin III. Urinary excretion of uroporphyrin, porphobilinogen (PBG), and delta aminolevulinic acid (ALA) increased. Liver content of protoporphyrin and uroporphyrin was also increased. Liver catalase was decreased in subjects with necrotic liver changes, which occurred with 1,2-DCB. Clinical observations included: anorexia and weight loss, hemiparesis (one rat on 1,4-DCB), weakness, ataxia, clonic contractions, hepatomegaly, severe liver damage with intense necrosis and fatty change (1,2-DCB) or degeneration and focal necrosis (1,4-DCB). No skin lesions were observed after testing for light sensitivity. 1,4-DCB was more porphyrogenic than 1,3-DCB. Of several chlorinated benzenes tested, those with para-positioning of chlorine atoms were the more porphyrogenic. The authors point out that mechanisms producing prophyrin derangements are different from those leading to heaptic necrosis. Of the two DCB's considered, 1,2-DCB was the more acutely toxic and liver-damaging, apparently reflecting the metabolism and formation of mercapturic acid, depleting sulfur-compound resources (e.g., glutathione) in the process (Rimington and Ziegler, 1963).

As noted previously, 1,3-DCB also induced hepatic prophyria in rats fed the compound daily by intubation at 800 mg/kg or 900 to 1,000 mg/kg (Poland, et al. 1971). The higher dose level produced porphyria similar to that reported by Rimington and Ziegler (1963), but the lower dose produced an initial porphyric response which then abated, probably as a result of the accompanying stimulation of liver microsomal drug metabolizing mechanisms.

Carlson and Tardiff (1976) studied the property of several halogenated benzenes to induce enzyme systems associated with the metabolism of foreign compounds. Rats were given daily oral doses of 10 to 40 mg/kg for 14 days. In this regimen, 1,4-DCB and other benzene derivatives decreased hexabarbital sleeping time during exposure and the effect persisted at least two weeks after treatment. Cytochrome c reductase, cytochrome P-450 content, glucuronyl transferase, benzpyrene hydroxylase, azoreductase, and detoxication of o-ethyl-o-p-nitrophenyl phenylphosphonothioate (EPN) were increased (most of them at the 20 and 40 mg/kg dose levels)(Ware and West, 1977).

Aryoshi, et al. (1975) and others have reported the induction of liver drug metabolizing enzyme systems in rats acutely fed chlorinated benzenes at 250 mg/kg. The three DCB isomers were highly metabolized, increased ALA synthetase, and are possible producers of epoxide intermediates (Ware and West, 1977, citing: Rimington and Ziegler, 1963; Poland, et al. 1971; Ariyoshi, et al. 1975; Williams, et al. 1975).

Rats injected intraperitoneally with 1,2-DCB at 735 mg/kg (5mmol/kg) showed an increase in bile duct pancreatic flow (Yang and Peterson, 1977). Injection of 1,2- and 1,4-DCB caused a reduction of bile duct pancreatic flow protein concentration, and increased hepatic bile flow.

Selected toxicity data for 1,2- and 1,4-DCB are summarized in Tables 7, 8, 9, and 10.

Synergism or Antagonism

There would appear to be many possibilities for synergistic and/or antagonistic actions among halogenated benzene compounds and between them and other compounds or conditions (Ware and West, 1977). DCB's have been shown to induce hepatic xenobiotic drug-metabolism systems and components (Ariyoshi, et al. 1975; Carlson and Tardiff, 1976), and the effects of DCB's have been shown to be modified by other chemical or biological factors (Salamone and Coppola, 1960; Totaro and LiCari, 1964; Gadrat, et al. 1962). An individual with existing liver damage or under the influence of another chemical (or hormone) which enhanced the metabolism of, say, 1,2-DCB into reactive, hepatoxic intermediates would be expected to be more than ordinarily susceptible to the DCB toxicity (Thompson, 1955). Conversely, a condition or other chemical that reduced metabolism of DCB to hepatoxic metabolites or provided essential materials to protect against harmful depletions (e.g., glutathione, lipotropic factors) would tend to ameliorate the direct cellular toxicity of absorbed DCB.

Table 7. - Acute toxicity of 1,2-DCB

Route	Conc. or Dose	Regimen	Subject	Effect	Reference
Inhal-	5,872 mg/m^3	7 hrs	Rat	Lethal in 4/5	e
ation	4,808 mg/m^3	24 hrs	G. pig.	LCLo	f
	4,808 mg/m^3	11-50 hrs	Rat	Irritation, eyes, nose; coma; death in 1/10; liver necrosis	e cit. g
	4,249 mg/m^3	7 hrs	Rat	LCLo	f
	3,239 mg/m^3	7 hrs	Rat	Eye irrit.; CNS depress.; liver, kidney damage	e
	300-4,808 mg/m^3	Few hrs.	Animals	Liver damage	c cit. g.
Oral	2,000 mg/kg	Single (oil)	G. pig.	Lethal to 100%	e
	1,875 mg/kg	"	Rabbit	Lethal to 50% (LD_{50})	l
	800 mg/kg	"	G. pig.	Survival, but weight loss.	e
	428 mg/kg	Daily, 3 days	Rat	Cumulative lethal toxicity; 1/5 LD_{50}	l
	324-649 mg/kg	Single	Rabbit	Lethal within 24 hrs.	b cit. g
	250 mg/kg	Daily	Rat	Increased liver metab. enzym. syst.	b cit. p
Intravenous	520 mg/kg	Single	Mouse	LDLo	f
	330 mg/kg	Single	Rabbit	$LDI_{L}o$	f
Subcut.	Unspecif.			Localized edema and necrosis	b cit. h
Dermal	Undil.	Appl. to skin 1/4-1 hr.	Human	Irritation; abnorm. pigmentation afterward lasting 3 mos.	e cit. h
	Unspec.	Skin appl. 2x/d x 5 applic.	Rat	Absorpt. of lethal amount	e cit. h
Eye	Undil., 2 drops	Single	Rabbit	Moderate pain; conjunct., irritation, clearing in 7 da.	e
Nose	600 mg/m^3	Single	Human	Strong odor; nasal and ocul. irritation; possible adaptation	a; e cit. n
	300 mg/m^3	Single	Human	Odor detectable; no irrit.	a, e

Table 8. - Long-term toxicity of 1,2-DCB

Route	Concentration or Dose	Regimen	Subject	Effect(s)	Reference
Inhal-	560 mg/m^3	7 h/d,5d/wk, 6-7 mo.	Rat, g. pig. rabbit.	No effect on several param.	e
	290 mg/m^3	7 h/d,5d/wk, 6.5 mo.	Rat, g. pig, mice.	No effect on several param.	e
	6-264 mg/m^3 (av. 90)	Plant expos., daily	Human	No evidence of organic or hematol. effect on clin. exam.	e
	455 mg/m^3 (tube)	Daily up to 15 days	Rat	Hepatic prophyria	r
Oral	376 mg/kg (tube)	5d/wk, 138 doses	Rat	Liver, kidney weight incr.; cloudy swelling in liver.	e
	188 mg/kg "	" "	Rat	Incr. liver and kidney wt.	e
	18.8 mg/kg "	" "	Rat	No effects noted	e
	0.01-0.1 mg/kg/day	5 mos.	Rat	Hematopoietic syst; altered cond. reflexes; incr. prothromb. time and altered enzyme activities.	l
Dermal	Expos. to liq. mixture	Repeated	Human	Sensitization, dermatitis (case report)	e
Subcut.	Unspecif.	Repeated	Rabbit	Blood dyscrasias, (agranulocytosis)	b

Note: See also Table 6 pertaining to human poisoning.

Table 9. - Acute toxicology of 1,4-DCB

Route	Concentration or Dose	Regimen	Subject	Effect(s)	Reference
Inhal-	10^5 mg/m^3	30 min., daily	Rabbit	CNS depression; ocul. and nasal irrit.	c cit. k
	" "	" "	Rat	Irritation, narcosis	c cit. k
	" "	" "	G. pig.	Irritation, CNS depression, deaths	c cit. k
	300-480 mg/m^3	Acute	Human	Painful irrit. to eyes and nose; acclimatization can occur.	a
	90-180 mg/m^3	Single	Human	Odor detection (strong odor at 180-360)	j
Oral	4,000 mg/kg	Single, 20 or 50 percent solution	Rat	LD_{100} -	j
	2,950 mg/kg	Single	Mouse	LD_{50}	c cit. k
	2,812 mg/kg	Single (oil)	Rabbit	LD_{50}	l
	2,800 mg/kg	Single, 50 percent soln.	G. pig	100 percent lethal	j
	1,600 mg/kg	Single, 50 percent soln.	G. pig	100 percent survival	j
	500 mg/kg	Single	Rat	LD_{50}	f
	300 mg/kg	Single	Human	Toxic dose	f
Intra-peritoneal	2,562 mg/kg	Single	Rat	LD_{50}	c cit. i
Subcut.	5,145 mg/l	Single	Mouse	LD_{50}	b cit. m
Skin	Contact with solid	Single	Human	Somewhat irritating. Burning sensation if contact is direct and prolonged. No apprec. abs. through skin.	a, j
	Strong fumes	Single or repeated	Human	May irritate in severe expos. conditions; no problem normally	j
Eye	Solid particles, vapor, fumes	Single	Human	Painful (also vapors at 300-480 mg/m^3 and severe at 960 mg/m^3.	j
Injection	5 mg.	Single	Rat	Occasionally, slight liver necrosis	c cit. g

Table 10. - Long term toxicity of 1,4-DCB

Route	Concentration or dose	Regimen	Subject	Effect(s)	Reference
Inhalation	10^5 mg/m^3	0.5 h/d,5-9da	Rabbit	Granulocytopenia; irrit.; CNS and lung tox.; deaths (12/18)	b cit. i
	4,800 "	8h/d, 5d/wk., up to 69 expos.	Rat, g. pig, rabbit	Severe irrit.; CNS depress. & collapse; liver, kidney, lung pathol.; deaths	j
	4,600-4,800 "	8hr/d 5d/wk	Rabbit	Tremors, weakness, nystagmus; some deaths	j cit. o
	2,050 "	7h/d, 5d/wk, 6 mos.	Rat, g. pig	Growth depression, incr. liver, kidney wt.; liver pathol. (necrosis, fatty degen., swelling, fibrosis)	j
	1,040 "	7h/d, 5d/wk, 16 da	Rat, g. pig	Incr. liver, kidney wt. (rat); lung, liver pathol.	j
	950 "	7h/d, 5d/wk 157-219 da	Rat, g. pig, rabbit, mouse, monkey	Growth depress. (g.p.); incr. liver, kidney weight; histol. liver changes (cloudy swelling, granular degen.) in rats	j
	300-1,020 " (ave. 630)	8h/d, 5d/wk, chron.	Human	Eye, nose irritation	j
	900 "	8h/d, 2wks	Mouse	Respir. excitation; liver pathol., deaths; at serum conc. 39mg/l.	m
	576 "	7h/d, 5d/wk, 6-7 mos.	Rat, g. pig, mice, rabbit, monkey	No adverse effects on several parameters	j
	480-960 "	Daily, occupational	Human	Painful irrit. of eyes, nose. Intolerable at more than 960 mg/m^3	j
	180-360 " (ave. 270)	Daily expos.	Human	Strong odor	j
	90-510"	Daily expos. (Occup.)	Human	No complaints or evidence of injury	j

Table 10. - Long-term Toxicity of 1,4-DCB - Continued

Route	Concentration or dose	Regimen	Subject	Effect(s)	Reference
Oral	1,000 mg/kg per dose (tube)	92 doses in 219 da	Rabbit	CNS depression; wt. loss; liver degen. and necrosis; deaths	j
	770 mg/kg/day	Up to 5 days	Rat	Hepatic porphyria	r
	500 mg/kg/day (tube)	5d/wk, 20 doses	Rat	Hepatic centrolobular necrosis; cloudy swelling, renal tubul. epith., and casts	j
	5,000 mg/kg doet	Up to 35 da	Peking duck	Death in 3/10. Retarded growth	j
	500 mg/kg/day (tube) "	5d/wk 263 doses in 367 da	Rabbit	CNS depress.; wt. loss; liver pathol.	j
	376 "	5d/wk 138 doses in 192 da	Rat	Incr. liver and kidney wt.; liver cirrhosis and focal necrosis.	j
	250 "	3 days	Rat	Induced liver metab. enzyme syst.	b cit. p
	188 "	5d/wk 138 doses in 192 da	Rat	Incr. liver and kidney wt.	j
	20-40 "	2 weeks	Rat	Induced liver metab. enzyme syst.	b cit. q
	18.8 "	5d/wk 138 doses in 192 da	Rat	No adverse effects detected	j

Note: See also Table 6 pertaining to human poisoning.

References used in Tables 7, 8, 9, 10

a. Patty, 1963

b. Ware and West, 1977

c. Am. Conf. Gov. Ind. Hyg., 1977

d. Occup. Safety Health Admin., 1976

e. Hollingsworth, et al. 1958

f. Christenson and Fairchild, 1976

g. Cameron, et al. 1937

h. Riedel, 1941

i. Zupko and Edwards, 1949

j. Hollingsworth, et al. 1956

k. Domenjoz, 1946

l. Varshavskaya, 1967a

m. Irie, et al. 1973

n. Elkins, 1950

o. Pike, 1944

p. Ariyoshi, et al. 1975

q. Carlson and Tardiff, 1976

r. Rimington and Ziegler, 1963

Teratology

Embryotoxicity and teratogenicity of DCB's apparently have not been studied and reported. A pregnant woman who developed mild, chronic erythrotoxic anemia from ingestion of 1,4-DCB-containing toilet air freshener blocks recovered after withdrawal and treatment and delivered an infant free of congenital abnormality (Campbell and Davidson, 1970). The potentiality for transplacental toxicosis or developmental effects may be inferred from evidence that lower chlorinated benzenes pass membrane barriers (including egg and placenta) and affect hormone-metabolizing systems (Ware and West, 1977).

Mutagenesis

The formation of an arene oxide metabolic intermediate has been associated with mutagenesis and carcinogenesis, and halobenzenes have been shown to form reactive intermediates (Ware and West, 1977).

Chromosomal and other nuclear derangements in roots of Allium exposed for four hours to 1,4-DCB vapors (resulting from placing 0.5 or 1.5 g in petri dish) were reported by Carey and McDonough (1943). Abnormal chromosome numbers were found in dividing nuclei, polyploidy was especially apparent in metaphase stages, and lagging chromosomes and dumbbell shaped nuclei were occasionally noted. The authors warned of the possibility of varietal instability if 1,4-DCB products were allowed to come in contact with buds.

Sharma and Bhattacharyya (1956) reported on experience with the use of 1,4-DCB solution in processing plant tissues for chromosome analyses. They indicated the potentiality of aqueous solutions causing chromosomal breakage and persistence of fragment-containing cells for several cell generations after treatment. Sharma and Sarkar (1957) reported on effects of 1,4-DCB solution on chromosomes of root tips, flower buds, and pollen grains of Nothoscordum fragrans Kunth. Saturated aqueous solution caused meta- and anaphase chromosome fragmentation in root tip cells, only chromosomal "stickiness" and non-disjunction in meiotic cells of flower buds, and no irregularities in pollen grain chromosomes.

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-DCB-treated root tips of Vicia faba, V. narbonensis, V. hirsuta, Pisum arvense, and Lathyrus sativus (Srivastava, 1966). These deviations from normal mitoses included: Shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells, chromosome bridges, and chromosome breakage (generally at heterochromatic regions). The author emphasized the potentiality of 1,4-DCB as a mutagenic substance.

Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether solution of 1,2-, 1,3-, and 1,4-DCB isomers increased the frequency of back-mutations (Prasad, 1970). Chlorination in the para position appeared to have special genetic significance.

Andersen, et al. (1972) found 1,2-DCB not to be mutagenic in an *in vitro* point mutation test system using several strains of histidine-requiring mutants of *Salmonella typhimurium*. Several compounds chemically similar to DCB's were also reported as negative in *Salmonella* mutagenicity tester strains (Simmon, et al. 1977). These were benzene, bromobenzene, 1,3- and 1,4-bromochlorobenzene, and parachlorotoluene.

Carcinogenesis

DCB (isomer not specified) gave negative results in a skin test of carcinogenicity (or cancer promoting ability) in mice (Guerin and Cuzin, 1961; Guerin, et al. 1971). Three- to four-month old Swiss mice in lots of four to eight (male and female) were treated topically three times with 0.1 ml of a solution of 10^4 mg DCB/l acetone. After 10 days the mice were euthanized and the treated skin area was examined for atrophy of sebaceous glands and for epithelial hyperplasia. On a scale of 0 to 4 (negative to very strongly positive) DCB was rated 0.9 and 0.7 on the sebaceous gland and hyperplasia criteria, respectively. This was interpreted as a negative result (not carcinogenic or cancer promoting).

In a later investigation using an *in vitro* carcinogenicity test system Guerin, et al. (1971) reported DCB as being negative again. This test involved treating a culture of rat pulmonary cells with test material and evaluating the inhibition of mitoses in cells fixed on slides after eight days. The test had been demonstrated as being able to detect known carcinogens, the correspondence between test results on mitotic inhibition and

carcinogenic versus noncarcinogenic chemicals being significant at the 1 percent level. The authors also reported good correlation between results of the lung cell mitosis inhibition test and those of the cutaneous test (sebaceous gland atrophy and epithelial hyperplasia) for various chemicals.

Ware and West (1977) have summarized a series of toxicity experiments by Hollingsworth, et al. (1956, 1968) in which toxicities of 1,2- and 1,4-DCB were studied in several animal species exposed by inhalation and gastric intubation to various dose levels over various periods of time. No tumors were reported in combined totals of 146 subjects exposed to 1,2-DCB or 189 exposed to 1,4-DCB. These were regarded as negative carcinogenicity results, but it should be pointed out that these studies were toxicity tests and were not designed to assess carcinogenicity. Small group sizes and relatively short durations render these studies' data inconclusive and inadequate for the assessment of carcinogenic properties of the DCB's. Further details of these experiments were discussed above in the toxicity subsection.

Varshavskaya (1967b) reported macroscopic, histologic, and histochemical data in rats exposed 9 months to 1,2-DCB (in oil, by tube) at daily dose levels of 0.1, 0.01, and 0.001 revealed no evidence of carcinogenic activity. Again, this experimentation (previously summarized in greater detail) was clearly not designed for the assessment of carcinogenicity. Although the exposure duration may be sufficient for some test models, the exposure levels were quite low and the group sizes (numbers of animals) were too small for valid detection and quantification of carcinogenesis.

Murphy and Sturm (1943) reported that repeated exposures to a relatively high concentration of 1,4-DCB vapors caused a reduction in the induced resistance to transplanted leukemia in rats. They tested four toxic agents (including 1,4-DCB) which they characterized as having been found to increase the leukemia rate in a strain of mice having a natural leukemia tendency (but no reference or details for this characterization were given). All four compounds- 1,4-DCB, Sodium pentobarbital, Sovasol (a purified naphtha), and amyl acetate - were positive in the leukemia resistance reduction test. Two other carcinogenic agents, x-ray and coal tar, had also been shown to modify induced resistance to transplantable tumors in mice (Murphy and Sturm, 1943, citing: Murphy and Maison, 1924; Murphy and Morton, 1915; Murphy and Taylor, 1918). Eighty-four percent of the activity control group (non-immunized) responded with leukemia ("takes") to the injected leukemia cells. Only 20 percent occurred in the immunized but untreated group. The immunized and treated (1,4-DCB vapor-exposed) group had 68 percent takes. About 40 young rats were used in each group. The toxic mechanism of the effect and its general applicability to distinguishing carcinogenic versus noncarcinogenic chemicals had not been determined.

Parsons (1942) reported that injections of 1,4-DCB (commercial, in sesame oil) along with injection of silica have induced early tumor formation in mice. In 6 irradiated mice a single dose of 0.2 ml of a 0.2 percent solution of 1,4-DCB (2,000 mg/l) in oil was injected subcutaneously, and 0.2 ml of silica in suspension was introduced at the injection site on the fourth day. One irradiated mouse received its injection intraperitoneally. On the

10th day the intraperitoneally treated mouse had ascites and, when euthanized, was found to have "widespread sarcomatous growth" throughout the peritoneum. This tumor gave 100 percent takes when grafted. Three of the irradiated mice died by the tenth day. Ten non-irradiated mice were injected subcutaneously with similar 1,4-DCB preparations for nine doses over two months, receiving also silica at two week intervals. Four of these died within 30 days. In one of the survivors a large sarcoma had developed (by the 77th day), with secondary growths in the lymph glands and peritoneum. Small group sizes and lack of further detail, especially concerning control groups, limit the usefulness of this data in assessing 1,4-DCB carcinogenicity.

Of the seven case reports of human poisoning by 1,2-DCB or products containing primarily 1,2-DCB (see Table 6) three involved diagnoses of neoplastic disease (leukemia: two acute myeloblastic, one chronic lymphoid). Although these data suggest the possibility of cancer-related hazard with exposure to 1,2-DCB, they fall very short of proving a cause-effect relationship and do not permit a quantitative risk assessment applicable to the general population.

Veljkovi'c' and Lalovi'c' (1977) examined the correlation between the quasi-valence number (Z*) and the known carcinogenic activity of a number of chemical compounds tested in animals and evaluated by IARC criteria. The Z* is a derived parameter recognizing valence electrons, atoms, and elements in the compound formula. The authors reported a strong correlation in the array of values examined, those with Z* below 3.20 corresponding to potential

carcinogens and those above noncarcinogens. DCB was evaluated as being in the potential carcinogen class with A Z* = 2.50.

No reports of specific carcinogenicity tests of DCB's in animals or of pertinent epidemiologic studies in humans were available.

Although strong direct evidence of carcinogenicity of DCB's is not at hand there seems to be a sufficient collection of varied data to suggest a prudent regard of the DCB's as suspected carcinogens, pending availability of better data. Apparently on the basis of the limited sarcoma induction data of Parsons (1942), 1,4-DCB was listed in the National Institute for Occupational Safety and Health Subfile of Suspected Carcinogens (Christensen and Lugenbyhl, 1975). The National Academy of Sciences (1977) found the lack of information "disturbing, in view of the suspected role of PDB in human leukemia and its apparent ability to undergo metabolic activation and covalent binding to tissue constitutents." The IARC Working Group (IARC, 1974) regarded the data on DCB's as of 1974, i.e., primarily those of Hollingsworth, Parsons, and Girard, as insufficient for assessing carcinogenic risk. Clearly, additional data is needed for a DCB carcinogenic risk evaluation, especially studies involving humans in pertinent exposure categories and animal studies under well designed protocols. 1,2- and 1,4-DCB have been selected for testing in the bioassay program of the National Cancer Institute (1978), and as of January 1978 a study of 1,4-DCB in mice was in progress at the Nagoya City University Medical School in Japan (IARC, 1978).

CRITERION FORMULATION

Existing Guidelines and Standards

The known current standards, guidelines, and goals for DCB's in air and water are summarized in Table 11. For air the only officially Federally regulated limits are by the Occupational Safety and Health Administration (29 CFR 1910 (Jan. 16, 1976) for 1,2-DCB and 1,4-DCB in workroom air at 300 mg/m^3 (ceiling) and 450 mg/m^3 (time-weighted average), respectively. The threshold limit value (TLV) guidelines of the American Conference of Governmental Industrial (1977) are virtually the same as the OSHA standards. These may need downward revision in view of human sensory responses in unacclimated persons. The Russian maximal allowable concentration (MAC) value for both 1,2-DCB and 1,4-DCB is 20 mg/m^3 (Int. Agency Res. Cancer, 1974, citing: Int. Labour Office, 1970), much lower than U.S. standards. The U.S. EPA (1977b) has published multimedia environmental goals (MEGs) for health related estimated permissible concentrations in air (EPC-AH): 1,2-DCB, 0.714 mg/m^3 (0.12 ppm) and 1,4-DCB, 1.07 mg/m^3 (0.18 ppm). The Russian and MEG Limits appear to recognize the following detection limits more closely than the OSHA and ACGIH values: 1,2-DCB, 12 to 24 mg/m^3 (odor threshold), 60 to 90 mg/m^3 (very noticeable odor), 150 to 180 mg/m^3 (unpleasant odor and eye irritation), 360 to 600 mg/m^3 (painful mucosal irritation); 960 mg/m^3 (painful irritation) (Am. Ind. Hyg. Assoc. 1964).

1,4-DCB is listed for inclusion among chemicals to be monitored by EPA under the Safe Drinking Water Act (40 CFR 141, Subpart E, PL 93-523).

The U.S. EPA (1977b) has published MEG's for health-related EPC's in water based on different approaches (see Table 11): (1) Derived from the air-health EPC extrapolated to water intake assuming daily intake and absorption efficiency values: EPA-WHI, 10.7 mg 1,2-DCB/l and 16.1 mg 1,4-DCB/l. (2) Based on considerations of maximum safe body concentration and biological half-life data: EPC-WH2, 4.4 mg 1,2-DCB/l and 6.21 mg 1,4-DCB/l. The reported maximum permisible concentrations (MPC's) in Russia, recognizing organoleptic factors (odor, taste) are much more conservative: 0.002 mg/l for both 1,2-DCB and 1,4-DCB (Varshavskaya, 1968: Stofen, 1973).

Apparently 1,3-DCB has been omitted from regulations or guidelines for media contamination, undoubtedly relecting its insignificant environmental contamination level and potential at this time. Practically speaking, it would seen reasonable to assume that efforts to contrtol the 1,2- and 1,4- isomers of DCB would also effectively control the 1,3-DCB as well, since it generally would accompany its isomers in total DCB contamination and would not have a significant contamination mode of its own.

Under the Federal Food, Drug and Cosmetic Act certain uses of both monochlorobenzene (MCB) and 1,4-DCB are regulated. MCB is a solvent in the manufacture of resins for food contact

TABLE 11

Standard, Criteria, or Goal Limits of Contamination for Dichlorobenzenes[a]

Medium	Standard, criterion, goal, etc.	1,2-DCB	1,4-DCB	Reference
Air	OSHA Standard for worker exposure	50 ppm (300 mg/m^3) (ceiling)	75 ppm (450 mg/m^3) (TWA)[b] (Car)[c]	A,B
	ACGIH recommended TLV	50 ppm (300 mg/m^3) (ceiling)	75 ppm (450 mg/m^3) (limit)	C
	EPA, MEG: EPC-AH1[d]	0.12 ppm (0.714 mg/m^3)	0.18 ppm (2.07 mg/m^3)	D
	Russian MAC (max. allow. conc.)	3.3 ppm (20 mg/m^3)	3.3 ppm (20 mg/m^3)	E
Water	EPA, MEG: EPC-WH1[e]	10.7 mg/l	16.1 mg/l	D
	WH2[f]	4.4 mg/l	6.21 mg/l	D
	Russian MPC[g]	0.002 mg/l	0.002 mg/l	F

A: Occup. Safety Health Admin. 1976. B: Christensen and Luginbyhl, 1975. C: ACGIH, 1977. D: U.S. EPA, 1977b. E: IARC, 1974. F: Stofen, 1973

[a]Current, based on available information. Note: No known regulatory standards exist in U.S. for any DCB isomers (1,2-, 1,3-, or 1,4-DCB) in ambient air or water; 1,3-DCB apparently omitted altogether

[b]Time weighted average, 8 hours

[c]Carcinogenicity notation in ref. B; carc. determination indefinite in A

[d]Estimated permissible concentration in air based on a model utilizing TLV

[e]Estim. permiss. conc. in water derived from EPC-ALL extrapolated to water intake

[f]Estim. permiss. conc. in water based on max. safe body conc. and biol. half-life considerations

[g]Maximum permissible concentration recognizing organoleptic effect

articles; residues in such resin products must not exceed 500 mg/kg. 1,4-DCB is an intermediate in the amnufacture of other resins for coating products in food contact use; in such products 1,4-DCB residues are limited to 0.8 mg/kg (32 Fr 14324 (Oct. 17, 1967); 34 FR 17332 (Oct. 25, 1969); 37 FR 22374 (Oct. 19, 1972). No imformation on regulation of residues or levels in food commodities was available.

The U.S. EPA has regulatory authority over some uses of DCB's under the Federal Environmental Pesticide Control Act of 1972. Registered under this act are 43 uses of 1,2-DCB and 304 uses of 1,4-DCB. The chlorinated benzene pesticides are categorized as Class III toxins (oral LD_{50} values ranging from 500 to 5,000 mg/kg and LC_{50} values ranging from 200 to 20,000 mg/m^3) and as such have a hazard signal ("caution") and precautionary labeling requirement: "Harmful if swallowed (inhaled or absorbed through skin). Avoid breathing vapors (dust or spray mist). Avoid contact with skin (eyes or clothing). In case of contact immediately flush eyes or skin with plenty of water. Get medical attention if irritation persists" (40 FR 28242 (July 3, 1975)).

The Department of Transportation (DOT) regulates interstate transport, and there are specific requirements in regard to handling DCB's as combustible materials (for which they are classified due to their toxic and flashpoint properties). The Coast Guard has regulatory authority for overseas transportation and has recognized toxic, aquatic life hazard, and combustible properties in requiring notifi-

cation of health, pollution and fire authorities in the event of spills. DCB's have been determined to be hazardous to aquatic alife in very low concentrations (Ware and West, 1977, citing U.S. Coast Guard, 1970).

Several states have or intend legislation regulating manufacture, use, disposal, handling, and/or registration and inventory of toxic/hazardous chemicals, foten mirroring Federal legislation and promulgations (Ware and West, 1977).

Current Levels of Exposure

In the few samples of relatively uncontaminated ground water and of drinking water the reported DCB levels ranged on the order of less than 0.001 to 0.003 mg/l. In the NCMS survey, median concentrations and frequency of positive samples in drinking water were low, compared to halomethanes. This data by itself would suggest a relatively low exposure level for the general public from drinking municipally treated water.

An attempt to estimate human DCB exposure doses by using available survey contaminant-level data and certain assumptions for water consumption and absorption efficiency is shown in Table 12. A spread of about 1,000 times between "minimal" and "maximal" case exposures resulted. Even so, less than "minimal" exposures may apply for some of the population (e.g., very pure water supply) and more than "maximal" exposure for others (highly contaminated supplies). Meaningful representative or typical values and limits defy precise definition at this time.

TABLE 12

Estimated Dichlorobenzene Exposure from Drinking Water*

Exposure Level	Exposure, mg			
	Daily uptake		Annual uptake	
	Per person	Per kg	Per person	Per kg
"Minimal" case:				
Median level in drinking water of 0.000005 mg/l (assume 3)	6×10^{-6}	0.086×10^{-6}	2.2×10^{-3}	0.031×10^{-3}
"Moderate" case:				
Assume level of 10^{-4} mg/l (33 x minimal, 1/33 x maximal).	200×10^{-6}	2.86×10^{-6}	73×10^{-3}	1.04×10^{-3}
"Maximal" case:				
Maximal reported level in drinking water of 0.003 mg/l	$6{,}000 \times 10^{-6}$	860×10^{-6}	$2{,}190 \times 10^{-3}$	31.3×10^{-3}

*Assuming human water consuption of 2 l/day, absorption efficiency of 100 percent, and body weight of 70 kg. Values probably about equally applicable to any single isomer, but not total of all. See exposure section for data base

TABLE 13

Estimated Dichlorobenzene Exposure
from Air Contamination

Exposure Level*	Estimated Exposure, mg+			
	Daily Uptake		Annual Uptake	
	Per Person	Per kg	Per Person	Per kg
"Minimal" case:				
1.5×10^{-3} mg/m^3 (lowest suburban concentration reported)	0.01725	0.000246	0.63	0.09
"Moderate" case:				
0.24 mg/m^3 (mean of all values reported from urban, suburban, and indoor air)	2.76	.0394	1,007	14
"Maximal" case:				
1.7 mg/m^3 (Reported in wardrobe air due to use of 1,4-DCB)	19.55	0.28	7,136	102

*Based on data of Morita and Ohi (1975) for 1,4-DCB

+Based on assumptions as follows: daily inspired volume for reference adult male, 23m^3 (Natl. Acad. Sci. 1978 citing: Int. Comm. Radiol. Prot. 1975); human body weight, 70 kg (NAS, 1978); absorption efficiency by inhalation, 50 percent

Specific data on ambient air contamination by DCB's was meager. Based on the data of Morita and Ohi (1975) at attempt is made to estimate levels of human exposure via air contamination (see Table 13).. The extent of the population that may be represented by the table values is simply unknown. Some segment may be subject to less exposure (e.g., remote rural dwelling), and some to more (e.g. highly contaminated urban or industrial area air, especially contaminate air associated with some occupations or perhaps indoor air where DCB products are used). Comparison of Tables 12 and 13 suggest greater intake doses via air than via water.

No data are available by which specific exposure to DCBs by consumption of food could be estimated. Reports of detectable, even significant levels in fish, meat, eggs, and grains representing direct-contamination residues or products of degradation of other chemicals would suggest the likelihood of at least some intake by ingestion of food (probably mostly from food of lipid nature because of food-chain lipophilic bioaccumulation processes).

Data indicate the possibility of dermal absorption from unusually high-level exposure to vapors or perhaps liquids, but this would likely be significant only in special individual circumstances. There are no data on the level or importance of dermal exposure for the general public, but it seems reasonable to speculate that it would be insignificant in relation to other exposure modes.

Special Groups at Risk

Persons with pre-existing pathology (hepatic, renal, central nervous system, blood) or metabolic disorders, who are taking certain drugs (hormones or otherwise metabolically active), or who are otherwise exposed to DCB's or related (chemically or biologically) chemicals by such means as occupation, or domestic use or abuse (e.g., pica or "sniffing") of DCB products, might well be considered at increased risk from exposure to DCB's.

Basis and Derivation of Criterion

There was not a sufficient weight of evidence from human or animal tests to qualitatively suggest that DCB's are carcinogenic or mutagenic in mammals or to derive a quantitative estimate of acceptable daily intake using cancer risk extrapolation methods. In addition, there were no human data to allow an estimation of the maximum daily oral dose producing no detected adverse effect.

The most usuable controlled experimental data on chronic enteric exposure in multiple animal species is that of Hollingsworth, et al. (1956, 1958). The maximum tested dose level producing no detectable adverse effects in these tests was 18.8 mg/kg/day over a period of six to seven months, for both 1,2-DCB and 1,4-DCB. Assuming the average weight of adult humans to be 70 kg, the average daily intake of water for man to be two liters, the ingestion of 18.7 grams of fish, a fish bioconcentration factor of 200 and applying an uncertainty factor of 1,000 (Nat. Acad. Sci. 1977), the acceptable

daily intake (ADI) of 1,2- or 1,4-DCB in man is calculated to be 1.316 mg/day ($\frac{18.8 \times 70}{1,000} = 1.316$). The corresponding no adverse effect ambient level in water would be 0.23 mg/l ($1.316 = x\ (2 + 200\ (0.0187))$). The similarity of toxicities among the DCB isomers indicates the applicability of this value to 1,3-DCB as well.

This calculation assumes that 100 percent of man's exposure is assigned to the ambient water pathway. The only environmental monitoring data available on the DCB's, inadequate as they are, suggest that man's exposure by inhalation of the material in air may be 3,000 to 15,000 times his exposure from water. Although it is desirable to arrive at a criterion level for water based on total exposure analysis, the data base for exposure pathways other than water is not sufficient to support a factoring of the ADI level calculated from ambient water assumptions.

The calculated level of 0.23 mg/l for any DCB isomer should be considered a total, i.e., total contamination by DCB isomers whether occurring singly or in combination should not exceed the criterion level. Pending the availability of better data on relative exposure by various routes and on carcinogenic risk, this level should be adequate to prevent adverse health effects from long-term ambient water exposures.

In summary based on the use of chronic toxicologic test data in animals, and an uncertainty factor of 1,000 the criterion level for DCB's (total) corresponding to the calculated total acceptable daily intake of 18.8 mg/kg, is 0.23 mg/l. Drinking water contributes 35 percent of

the assumed exposure while eating contaminated fish products accounts for 65 percent.

The criterion level for DCB can alternatively be expressed as 0.35 mg/l if exposure is assumed to be from the consumption of fish and shellfish products alone.

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